CLINICAL APPROPRIATENESS GUIDELINES

SPECIALTY LABORATORY MEDICINE

Appropriate Use Criteria

EFFECTIVE JANUARY 01, 2021
Proprietary

Approval and implementation dates for specific health plans may vary. Please consult the applicable health plan for more details.

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8600 West Bryn Mawr Avenue
South Tower – Suite 800 Chicago, IL 60631
www.aimspecialtyhealth.com

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Description and Application of the Guidelines

The AIM Clinical Appropriateness Guidelines (hereinafter "the AIM Clinical Appropriateness Guidelines" or the "Guidelines") are designed to assist providers in making the most appropriate treatment decision for a specific clinical condition for an individual. As used by AIM, the Guidelines establish objective and evidence-based criteria for medical necessity determinations where possible. In the process, multiple functions are accomplished:

- To establish criteria for when services are medically necessary
- To assist the practitioner as an educational tool
- To encourage standardization of medical practice patterns
- To curtail the performance of inappropriate and/or duplicate services
- To advocate for patient safety concerns
- To enhance the quality of health care
- To promote the most efficient and cost-effective use of services

The AIM guideline development process complies with applicable accreditation standards, including the requirement that the Guidelines be developed with involvement from appropriate providers with current clinical expertise relevant to the Guidelines under review and be based on the most up-to-date clinical principles and best practices. Relevant citations are included in the References section attached to each Guideline. AIM reviews all of its Guidelines at least annually.

AIM makes its Guidelines publicly available on its website twenty-four hours a day, seven days a week. Copies of the AIM Clinical Appropriateness Guidelines are also available upon oral or written request. Although the Guidelines are publicly-available, AIM considers the Guidelines to be important, proprietary information of AIM, which cannot be sold, assigned, leased, licensed, reproduced or distributed without the written consent of AIM.

AIM applies objective and evidence-based criteria, and takes individual circumstances and the local delivery system into account when determining the medical appropriateness of health care services. The AIM Guidelines are just guidelines for the provision of specialty health services. These criteria are designed to guide both providers and reviewers to the most appropriate services based on a patient's unique circumstances. In all cases, clinical judgment consistent with the standards of good medical practice should be used when applying the Guidelines. Guideline determinations are made based on the information provided at the time of the request. It is expected that medical necessity decisions may change as new information is provided or based on unique aspects of the patient's condition. The treating clinician has final authority and responsibility for treatment decisions regarding the care of the patient and for justifying and demonstrating the existence of medical necessity for the requested service. The Guidelines are not a substitute for the experience and judgment of a physician or other health care professionals. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

The Guidelines do not address coverage, benefit or other plan specific issues. If requested by a health plan, AIM will review requests based on health plan medical policy/guidelines in lieu of the AIM Guidelines.

The Guidelines may also be used by the health plan or by AIM for purposes of provider education, or to review the medical necessity of services by any provider who has been notified of the need for medical necessity review, due to billing practices or claims that are not consistent with other providers in terms of frequency or some other manner.

General Clinical Guideline

Clinical Appropriateness Framework

Critical to any finding of clinical appropriateness under the guidelines for a specific diagnostic or therapeutic intervention are the following elements:

- Prior to any intervention, it is essential that the clinician confirm the diagnosis or establish its pretest likelihood based on a complete evaluation of the patient. This includes a history and physical examination and, where applicable, a review of relevant laboratory studies, diagnostic testing, and response to prior therapeutic intervention.
- The anticipated benefit of the recommended intervention should outweigh any potential harms that may result (net benefit).
- Current literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- Based on the clinical evaluation, current literature, and standards of medical practice, there exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

If these elements are not established with respect to a given request, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would supersede the requirements set forth above. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account.

Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

Requests for multiple diagnostic or therapeutic interventions at the same time will often require a peer-to-peer conversation to understand the individual circumstances that support the medical necessity of performing all interventions simultaneously. This is based on the fact that appropriateness of additional intervention is often dependent on the outcome of the initial intervention.

Additionally, either of the following may apply:

- Current literature and/or standards of medical practice support that one of the requested diagnostic or therapeutic interventions is more appropriate in the clinical situation presented; or
- One of the diagnostic or therapeutic interventions requested is more likely to improve patient outcomes based on current literature and/or standards of medical practice.

Repeat Diagnostic Intervention

In general, repeated testing of the same anatomic location for the same indication should be limited to evaluation following an intervention, or when there is a change in clinical status such that additional testing is required to determine next steps in management. At times, it may be necessary to repeat a test using different techniques or protocols to clarify a finding or result of the original study.

Repeated testing for the same indication using the same or similar technology may be subject to additional review or require peer-to-peer conversation in the following scenarios:

- Repeated diagnostic testing at the same facility due to technical issues
- Repeated diagnostic testing requested at a different facility due to provider preference or quality concerns
- Repeated diagnostic testing of the same anatomic area based on persistent symptoms with no clinical change, treatment, or intervention since the previous study
- Repeated diagnostic testing of the same anatomic area by different providers for the same member over a short period of time

Repeat Therapeutic Intervention

In general, repeated therapeutic intervention in the same anatomic area is considered appropriate when the prior intervention proved effective or beneficial and the expected duration of relief has lapsed. A repeat intervention requested prior to the expected duration of relief is not appropriate unless it can be confirmed that the prior intervention was never administered.

Specialty Laboratory Medicine

General Information/Overview

Scope

These guidelines address laboratory medicine and clinical pathology, including tests which establish the diagnosis of disease or inform the selection of therapy from bodily fluids using biochemistry, molecular pathology, and hematology[1]. While these guidelines apply to a variety of specialty laboratory tests managed by AIM, genetic sequencing tests are covered separately by AIM's genetic testing guideline (available at https://aimspecialtyhealth.com/resources/clinical-guidelines/genetic-testing/)

For interpretation of the Guidelines, and where not otherwise noted, "adult" refers to persons age 19 and older, and "pediatric" refers to persons age 18 and younger. Where separate indications exist, they are specified as **Adult** or **Pediatric**. Where not specified, indications and prerequisite information apply to persons of all ages.

See the Coding section for a list of modalities included in these guidelines. Codes that are not listed in this section are outside the scope of AIM's laboratory medicine guideline.

Definitions

BBDRisk Dx is an immunohistochemistry (IHC) assay of 4 cancer markers (MMP1, CEACAM6, HYAL1, and HEC1) of formalin fixed paraffin embedded (FFPE) tissue in women with atypical or usual hyperplasias, sclerosing adenosis, papillomas, or a combination of any of these types of abnormalities to assess the level of risk for developing breast cancer. The Cancer Risk Score ranges from 0-10 with higher scores corresponding to higher risk of subsequent cancer development.

- Low Risk < 0.5
- Intermediate Risk > 0.5 and ≤ 5.4
- High Risk > 5.4

BLOODchip ID is a genotyping platform based on Luminex R xMAP technology for simultaneous determination of 37 red blood cell (RBC) antigens (ID CORE XT) and 18 human platelet antigens (HPA) (ID HPA XT) using the BIDS XT software[2]

Chemo-FX is an in vitro chemosensitivity and resistance assays developed as a method to select the optimal chemotherapy regimen (sensitivity assays) or identify those agents least likely to be effective (resistance assays). ChemoFx is a cell culture-based chemoresponse assay that measures the sensitivity of tumor-derived malignant epithelial cells to chemotherapeutic agents in vitro, using quantification of cellular DNA as the assay endpoint.

Four Kallikrein (4Kscore) combines four prostate-specific biomarkers (Total PSA, Free PSA, Intact PSA, and human kallikrein 2 [hK2]) with clinical factors (age, prior biopsy status, and optional DRE) to predict the risk of high-grade prostate cancer (Gleason 7 or higher) and categorizes long-term risk of prostate cancer metastasis and mortality. The 4Kscore Test is indicated after an abnormal PSA and/or DRE, prior to the first biopsy or after a negative biopsy, to assist with making a prostate biopsy decision. References ranges for the 4K test are as follows:

- Low risk: 4Kscore result < 7.5%
- Intermediate Risk: 4Kscore result 7.5%-19%
- High Risk: 4Kscore result ≥ 20%

Prostate Cancer Risk Panel is a FISH analysis of 4 genes (ASAP1, HDAC9, CHD1, and PTEN) and incorporation into an algorithm of the biopsy specimen to determine the probability of higher tumor grade.

OVA1 (also referred to as the multivariate index assay) is a test that includes five serum biomarkers (Beta-2 microglobulin, Transferrin, Transthyretin, Apolipoprotein A1 and CA 125) approved by the US Food and Drug Administration (FDA) in 2009 to further assess the likelihood of malignancy in women who are planning to have surgery for an adnexal mass. OVA1 test scores range from 0-10. Triglyceride levels exceed 4.5 g/L or rheumatoid factor levels ≥ 250 international units/mL may interfere with the accuracy of the test.

- Premenopausal women
  - Low probability of malignancy: OVA1 < 5.0
  - High probability of malignancy: OVA1 ≥ 5.0
- Postmenopausal women
  - Low probability of malignancy: OVA1 < 4.0
  - High probability of malignancy: OVA1 ≥ 4.4

Overa (also known as OVA2) is a second generation multivariate index assay approved by the FDA in 2016. This test utilizes CA 125 II, human epididymis protein 4 (HE4), apolipoprotein A1, follicle-stimulating hormone, and transferrin. Overa is generally used as a reflex test when OVA1 produces intermediate results. Overa test scores range from 0-10. Indications for use are the same as for OVA1.

- Low risk of malignancy < 5.0
- High risk of malignancy ≥ 5.0

Risk of Malignancy Algorithm (ROMA) is a qualitative serum test (CA 125 and HE4) that was approved by the US Food and Drug Administration (FDA) in 2011 to further assess the likelihood of malignancy in women who are planning to have surgery for an adnexal mass. ROMA interprets the results using two separate logistic regression algorithms based on menopausal status from a score of 0-10.

- Premenopausal women
  - High risk of malignancy ≥ 1.31
- Postmenopausal women
  - High risk of malignancy ≥ 2.77

VeriStrat is a blood-based proteomic test that is intended as a prognostic tool for predicting survival for standard therapies used in the treatment of NSCLC, as well as a predictive tool for response to EGFR TKIs. The VeriStrat assay uses an 8-peak proteomic signature; 4 of the 8 have been identified as fragments of serum amyloid A protein 1. This protein has been found to be elevated in individuals with a variety of conditions associated with acute and chronic inflammation. The VeriStrat assay measures acute phase proteins and the acute phase response which indicates chronic inflammation and more aggressive cancer. Results are reported as either VeriStrat good or poor: VeriStrat Good results indicate a disease state that is more likely to respond to standard of care treatment while VeriStrat Poor results indicate a chronic inflammatory disease state. Biodesix, the laboratory preforming VeriStrat, suggests that patients with Veristart Poor disease may benefit from clinical trials, novel combinations of therapies, genomic profiling, or earlier initiation of therapy.

Fibrosure/Fibrotest combines serum hepatocellular biomarkers with proprietary algorithms to measure the extent of fibrosis

- HCV FibroSURE /(FibroTest) and the FibroTest-ActiTest uses a combination of six serum hepatocellular biomarkers (α2-macroglobulin, haptoglobin, bilirubin, γ-glutamyl transpeptidase (GGT), apolipoprotein AI, and Alanine Aminotransferase (ALT)) plus age and sex in a proprietary algorithm to measure of fibrosis in patients with HCV related liver disease. The FibroTest combines the first five biomarkers to measure the degree of hepatic fibrosis and generates a score ranging from F0 (none) to F4 (severe). The ActiTest uses ALT in combination with the other five hepatic biomarkers to assess hepatic inflammatory activity and generates a score ranging from A0 (no activity) to A3 (severe activity)

- ASH FibroSURE/(ASH Test) uses a combination of 10 serum hepatocellular biomarkers (α2-macroglobulin, haptoglobin, apolipoprotein AI, bilirubin, GGT, ALT, AST, total cholesterol, triglycerides, and fasting glucose) of liver function together with age, sex, height, and weight in a proprietary algorithm to measure the risk of fibrosis in patients with Alcoholic liver disease
- NASH FibroSURE /NASH FibroSURE (NASH Test) uses combination of 10 of serum hepatocellular biomarkers (α2-macroglobulin, haptoglobin, apolipoprotein AI, bilirubin, GGT, ALT, AST, total cholesterol, triglycerides, and fasting glucose) in combination with age, sex, height, and weight to measure the risk of fibrosis in patients with non alcoholic steatohepatitis

Phases of the care continuum are broadly defined as follows:

- **Screening** – testing in the absence of signs or symptoms of disease
- **Diagnosis –** testing based on a reasonable suspicion of a particular condition or disorder, usually due to the presence of signs or symptoms
- **Management –** testing to direct therapy of an established condition, which may include preoperative or postoperative imaging, or imaging performed to evaluate the response to nonsurgical intervention
- **Surveillance –** periodic assessment following completion of therapy, or for monitoring known disease that is stable or asymptomatic

Statistical terminology

- **Confidence interval (CI) –** range of values which is likely to contain the cited statistic. For example, 92% sensitivity (95% CI, 89%-95%) means that, while the sensitivity was calculated at 92% on the current study, there is a 95% chance that, if a study were to be repeated, the sensitivity on the repeat study would be in the range of 89%-95%.
- **Diagnostic accuracy –** ability of a test to discriminate between the target condition and health. Diagnostic accuracy is quantified using sensitivity and specificity, predictive values, and likelihood ratios.
- **Hazard ratio –** odds that an individual in the group with the higher hazard reaches the outcome first. Hazard ratio is analogous to odds ratio and is reported most commonly in time-to-event analysis or survival analysis. A hazard ratio of 1 means that the hazard rates of the 2 groups are equivalent. A hazard ratio of greater than 1 or less than 1 means that there are differences in the hazard rates between the 2 groups.
- **Likelihood ratio –** ratio of an expected test result (positive or negative) in patients *with* the disease to an expected test result (positive or negative) in patients *without* the disease. Positive likelihood ratios, especially those greater than 10, help rule in a disease (i.e., they substantially raise the post-test probability of the disease, and hence make it very likely and the test very useful in identifying the disease). Negative likelihood ratios, especially those less than 0.1, help rule out a disease (i.e., they substantially decrease the post-test probability of disease, and hence make it very unlikely and the test very useful in excluding the disease).
- **Odds ratio –** odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. An odds ratio of 1 means that the exposure does not affect the odds of the outcome. An odds ratio greater than 1 means that the exposure is associated with higher odds of the outcome. An odds ratio less than 1 means that the exposure is associated with lower odds of the outcome.
- **Predictive value –** likelihood that a given test result correlates with the presence or absence of disease. Positive predictive value is defined as the number of true positives divided by the number of test positives. Negative predictive value is defined as the number of true negatives divided by the number of test negative patients. Predictive value is dependent on the prevalence of the condition.

- **Pretest probability –** probability that a given patient has a disease prior to testing. May be divided into very low (less than 5%), low (less than 20%), moderate (20%-75%), and high (greater than 75%) although these numbers may vary by condition.
- **Relative risk –** probability of an outcome when an exposure is present relative to the probability of the outcome occurring when the exposure is absent. Relative risk is analogous to odds ratio; however, relative risk is calculated by using percentages instead of odds. A relative risk of 1 means that there is no difference in risk between the 2 groups. A relative risk of greater than 1 means that the outcome is more likely to happen in the exposed group compared to the control group. A relative risk less than 1 means that the outcome is less likely to happen in the exposed group compared to the control group.
- **Sensitivity –** conditional probability that the test is positive, given that the patient has the disease. Defined as the true positive rate (number of true positives divided by the number of patients with disease). Excellent or high sensitivity is usually greater than 90%.
- **Specificity –** conditional probability that the test is negative, given that the patient does not have the disease. Defined as the true negative rate (number of true negatives divided by the number of patients without the disease). Excellent or high specificity is usually greater than 90%.

Clinical Indications

The following section includes indications for which specialty labs are considered medically necessary, along with prerequisite information and supporting evidence where available.

Oncologic lab testing

Four Kallikrein (4K) Score

Advanced imaging is considered medically necessary for management when **ALL** of the following criteria are met:

- Prostate cancer is suspected in **EITHER** of the following scenarios:
  - Abnormal PSA (PSA > 3 ng/dL in men 40-75 years old OR PSA > 4ng/dL > 75 years old)
  - Suspicious DRE
- Multiparametric prostate MRI has not been performed as part of the episode of care
- Other validated lab test* including the prostate health index (PHI), PCA3 assay, and ConfirmMDx have not been performed as part of the episode of care
- Results will determine whether an initial biopsy or single repeat biopsy will be performed
- Not on Biotin supplementation (> 5 mg/day)
- No established diagnosis of prostate cancer
- No use of 5-alpha reductase medication within previous 6 months
- No prostate procedure, including biopsy, within the previous 6 months

**Note: does not include the prostate serum antigen (PSA) test*

Rationale [3-24]

Prostate cancer is the most common cause of malignancy in men in the United States. In 2020, 191,000 new cases will be diagnosed and 33,000 people will die of this disease. Multiple randomized trials provide evidence suggesting that screening does confer a small absolute benefit for reducing prostate cancer mortality and the risk of developing metastatic disease. Unfortunately, screening can often times result in false positives as well as over diagnosis of otherwise clinically indolent prostate cancer. Both imaging (e.g. multiparametric MRI) and specialty lab testing (e.g.

4KScore Test, prostate health index PHI, PCA3 assay, and ConfirmMDx) have been utilized for risk-stratification of prostate cancer patients to determine when more invasive procedures are appropriate.

The 4Kscore Test combines four prostate-specific biomarkers (Total PSA, Free PSA, Intact PSA, and human kallikrein 2 [hK2]) with clinical factors (age, prior biopsy status, and optional DRE) to predict the risk of high-grade prostate cancer (Gleason 7 or higher), and is indicated for patients with an abnormal PSA and/or DRE, prior to the first biopsy or after a negative biopsy. Long-term risk of prostate cancer metastasis and mortality are divided into three categories:

- Low risk: 4Kscore result < 7.5%
- Intermediate Risk: 4Kscore result 7.5%-19%
- High Risk: 4Kscore result ≥ 20%

A prostate biopsy should be considered in men in the intermediate and high risk range. In addition, biotin supplementation as well as recent digital rectal exam (within 4 days), 5-alpha reductase inhibitor therapy (within 6 months), and invasive prostate procedure (within 6 months) may affect the accuracy of the test and are not recommended by the reference lab. The 4KScore Test is not intended for patients with a previous diagnosis of prostate cancer.

Screening

Data is insufficient to recommend the 4KScore Test as a screening tool. In one prospective, observational trial designed to assess the relationship between diet and incident cancer, the authors measured 4K markers in the blood of 1223 prostate cancer cases and 3028 controls. The predictive accuracy was enhanced by the 4KScore Test compared with PSA alone (0.80 vs 0.73; improvement 0.07; 95% CI, 0.04-0.10). Approximately half of men over 60 years of age with an elevated PSA had a low 4KScore--translating into 1.7% risk of prostate cancer death at 15 years. The trial however does not sufficiently address the enhanced impact of the 4KScore for earlier detection of prostate cancer with change in treatment strategy and benefit in survival. The 4KScore test is not recommended by medical specialty societies (NCCN, AUA, USPSTF, and CAU) as a screening tool for prostate cancer.

Risk stratification for abnormal PSA and/or DRE, prior to the first biopsy or after a negative biopsy, to guide prostate biopsy decision.

A large body of evidence supports the use of the 4KScore test to risk-stratify men with an abnormal PSA and/or DRE, prior to the first biopsy or after a negative biopsy. In a representative 2017 systematic review and meta-analysis of twelve clinical validation studies comprised of 11,134 patients, the pooled AUC to discriminate for high-grade PCa for all 12 studies was 0.81 (fixed effects 95% CI, 0.80-0.83). The impact of 4KScore Test on planned biopsies ranged from 25%-82% with a median reduction of biopsies in 49% of patients as reported in a 2018 systematic review. Multiple prospective and retrospective trials corroborate efficacy for detecting clinically significant cancer in patients with elevated PSA and/or DRE. No difference in diagnostic accuracy is seen in patients in the diagnostic gray-zone (PSA 10-25 ng/dL) or African Americans patients. The 4KScore test is generally supported by medical specialty societies (NCCN, AUA, and CAU) in this clinical scenario.

Concurrent use of multiple biomarker tests and/or multiparametric MRI

Evidence is insufficient to endorse concurrent use of multiple prostate biomarker tests and/or mpMRI. Biomarker testing available prior to biopsy include percent free PSA (%f PSA), Prostate Health Index (PHI), 4Kscore, or EPI in patients with PSA levels > 3 ng/mL, as well as %f PSA, PHI, 4Kscore, EPI, PCA3, and ConfirmMDx in patients with at least one prior negative biopsy. In a 2018 systematic review and meta-analysis comparing utility of six prognostic biomarkers, only PHI and the 4Kscore present LOE = 1 for discriminating between aggressive and indolent prostate tumors with an additional value compared to the classical parameters. As reported in non-comparative studies, the discriminatory power of the 4Kscore seems to be higher than that of the PHI. In a 2017 systematic review and meta-analysis, the pooled data showed the derived area under the curve (AUC) from the hierarchical summary receiver operating characteristic (HSROC) showed an accuracy of 0.76 and 0.72 for detecting prostate cancer and an accuracy of 0.82 and 0.81 for detecting high grade prostate cancer in the PHI and 4KScore test, respectively. The use of multiple concurrent biomarker tests has not been evaluated, and cannot be recommended.

The PROMIS trial compared the mpMRI and TRUS biopsy in biopsy naïve patients with elevated PSA, abnormal DRE, or a positive family history. The authors reported MRI was more sensitive than TRUS biopsy for clinically significant cancer (93% vs 48%), and had a higher NPV (89% vs 74%). The specificity (41% vs 96%) and positive predictive value (51% vs 90%) was lower for mpMRI and TRUS biopsy, respectively. If biopsy was deferred in low-suspicion MRIs, biopsy could have been avoided in 27% of patients and would have missed only 5% of the clinically significant cancers. In a single institution retrospective trial of patients who received both mpMRI and 4KScore testing, the area under the curve (AUC) for using the 4Kscore test and mpMRI together 0.82 (0.75±0.89) was superior to using the 4KScore test 0.70 (0.62±0.79) or mpMRI 0.74 (0.66±0.81) alone (P = .001). Additional trials are needed to support use of concurrent biomarker and mpMRI to risk stratify patients with suspected prostate cancer.

4KScore prior to radical prostatectomy

Evidence is insufficient to support use of 4KScore test to risk stratify patients prior to radical prostatectomy. In a small prospective trial, higher 4Kscores were associated with higher grade at radical prostatectomy. In a cohort study of 392 screened in the Rotterdam arm of the European Randomized Study of Screening for Prostate Cancer who were diagnosed with prostate cancer because of an elevated PSA ≥3.0 ng/ml and were treated with RP, the base model had

an AUC of 0.81, while the 4K Score had an AUC of 0.84 (P < .0005) for predicating high-risk disease. These trials however are markedly limited by overall size and does not sufficiently address change in treatment strategy and benefit in survival. The 4KScore test is not recommended by medical specialty societies (NCCN, AUA, CAU) as a risk-stratification tool prior to radical prostatectomy.

OVA1

Adults

OVA1 is considered medically necessary for the preoperative evaluation of an indeterminate adnexal mass when **ALL** of the following criteria are met:

- Adnexal mass is indeterminate based on clinical and complete pelvic ultrasound* evaluation
- Test will determine the required surgical approach, operator expertise or level of care

**Note: Complete pelvic ultrasound includes both trans-abdominal and trans-vaginal technique*

Rationale[4-37]

Adnexal masses, most commonly found in the ovaries and fallopian tubes, are a common gynecological problem effecting 5%-10% of all women in the US. The differential diagnosis is broad and may include benign causes (related to the menstrual cycle and hormonal to stimulation), cysts, acute causes (ectopic pregnancy, rupture, or infection), or neoplastic etiologies. The cornerstone of evaluation is a history and physical as well as imaging studies. In the work-up for malignancy, serum biomarkers may contribute to the evaluation although utility is limited. Biomarkers that have been marketed as a tool to help differentiate benign from malignant causes of adnexal masses include OVA1, OVERA, and the Risk of Malignancy Algorithm.

OVA1 (also referred to as the multivariate index assay) is a test that includes five serum biomarkers (Beta-2 microglobulin, Transferrin, Transthyretin, Apolipoprotein A1, and CA 125) to further assess the likelihood of malignancy in women who are planning to have surgery for an adnexal mass. OVA1 test scores range from 0-10. Triglyceride levels exceed 4.5 g/L or rheumatoid factor levels ≥ 250 international units/mL may interfere with the accuracy of the test.

- Premenopausal women
  - Low probability of malignancy: OVA1 < 5.0
  - High probability of malignancy: OVA1 ≥ 5.0
- Postmenopausal women
  - Low probability of malignancy: OVA1 < 4.4
  - High probability of malignancy: OVA1 ≥ 4.4

OVERA (also known as OVA2) is a second generation multivariate index assay that utilizes CA 125 II, human epididymis protein 4 (HE4), apolipoprotein A1, follicle-stimulating hormone, and transferrin to assess whether a woman who presents with an ovarian adnexal mass is at high or low likelihood of finding malignancy as part of the preoperative evaluation. Overa is generally used as a reflex test when OVA1 produces indeterminate results. Overa test scores range from 0-10.

- Low risk of malignancy < 5.0
- High risk of malignancy ≥ 5.0

<u>Screening</u>

Data is insufficient to recommend either OVA1 or OVERA for use as a screening tool. In a retrospective trial evaluating the several biomarkers (apolipoprotein A1, truncated transthyretin, transferrin, hepcidin, β-2 microglobulin, connective tissue activating protein III, and interalpha-trypsin inhibitor heavy-chain 4) alone and in combination with CA 125, CA 125 levels were elevated (≥ 35 U/mL) in 61.5% of 65 patients who within 1 year before the diagnosis of cancer. The additional the 7 other biomarkers failed to improve the sensitivity of CA 125 alone. In a trial also utilizing serum specimens from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, 28 ovarian cancer biomarkers were evaluated as potential candidates for ovarian cancer screening. Of the top performing markers, CA125, HE4, transthyretin, CA15.3, and CA72.4 had a sensitivity of 95% and specificity ranging from 0.73 to 0.40. CA125 remained the single best biomarker for ovarian cancer and has its strongest signal within 6 months of diagnosis. The OVA1 and OVERA tests are not recommended by FDA or medical specialty societies (NCCN and SGO) as a screening tool for ovarian cancer.

<u>OVA-1 or OVERA with adnexal mass and surgery is NOT planned</u>

Insufficient data to recommend either OVA1 or OVERA for use as a risk-stratification tool in patients with an adnexal mass and surgery is not planned. Both the OVA1 and OVERA trials prompting FDA approval of these tests included women with planned surgery. As such, the FDA specifically approved these tests as part of the preoperative evaluation

to aid in assessing whether a woman who presents with an ovarian adnexal mass is at high or low likelihood of finding malignancy at surgery. The OVA1 and OVERA tests are not meant to supplant clinical judgement for evaluation of ovarian cancer. The OVA1 and OVERA tests are not recommended by the FDA or medical specialty societies (NCCN, SGO, ACOG) in women with adnexal masses where surgery is not planned.

OVA-1 for preoperative evaluation of an indeterminate adnexal mass

Evidence is sufficient to recommend OVA1 for use as a risk-stratification tool in patients with an adnexal mass and when surgery is planned. In the prospective, multi-institutional (OVA1) trial of female patients scheduled to undergo surgery, OVA1 alone had a sensitivity of 93% and NPV of 97%; both endpoints improved when physician assessment and OVA1 were combined (96% and 98%). However the combination of physician assessment and OVA1 also decreased the specificity and PPV. An additional trial in women who had imaging and biomarker analysis showed that MIA combined with clinical assessment had significantly higher sensitivity (95.3%; 95% CI, 88.6%-98.2%) compared to clinical assessment alone (68.6%; 95% CI, 58.2%-77.4%), CA 125-II (62.8%; 95% CI, 52.2%-72.3%), and modified ACOG guidelines (76.7%; 95% CI, 66.8%-84.4%) (P < .0001). This improvement was seen regardless of menopausal status. In a merged analysis of 2 related prospective, multi-institutional (Bristow et al and Ueland et al.) trial, patients with planned surgery for adnexal mass had biomarker and imaging results correlated with surgical findings. Of the 1110 women who were enrolled with an adnexal mass on imaging, 1024 cases were evaluable. High-risk findings were present in 46% of 1232 imaging tests and 61% of 1024 MIA tests. Sensitivity and specificity for the prediction of malignancy were 98% (95% CI, 92%-99%) and 31% (95% CI, 27%-34%) for ultrasound or MIA; 68% (95% CI, 58%-775) and 75% (95% CI, 72%-78%) for ultrasound and MIA, respectively. For computed tomography scan or MIA, sensitivity was 97% (95% CI, 92%-99%) and specificity was 22% (95% CI, 16%-28%); the sensitivity and specificity for computed tomography scan and MIA were 71% (95% CI, 62%-79%) and 70% (95% CI, 63%-76%). Only 1.6% of ovarian tumors were malignant when both tests indicated low risk. Although there is some evidence for OVA1 as an independent predictive marker for ovarian cancer, the lack of detailed specifics of clinical assessment defined in the trials precludes interpretation as imaging is optional. In addition the ACOG guidelines for “Evaluation and Management of Adnexal Masses” recommends imaging as part of the standard evaluation. The OVA1 is specifically recommended by NCCN for assessment of patients who should undergo surgery by an experienced gynecologic oncologist and who can have surgery in the community. The SGO and ACOG make more generalized states of the utility of serum biomarker panels in this clinical scenario.

OVERA for preoperative evaluation of an indeterminate adnexal mass[25-38]

Insufficient evidence to recommend OVERA for use as a risk-stratification tool in patients with an adnexal mass and surgery is planned. In a publication using banked serum samples to develop OVERA followed with clinical validation in the prospective OVA500 trial of patients who underwent surgery to remove an adnexal mass, OVERA specificity (69%, 277/401 [n/N]; 95% CI, 64.4%-73.4%) and PPV (40%, 84/208; 95% CI, 33.9%-47.2%) were significantly improved over OVA1 (specificity, 54%, 215/401; 95% CI, 48.7%-58.4%, and PPV, 31%, 85/271; 95% CI, 26.1%-37.1%, respectively) in this cohort. Sensitivity and NPV were not significantly different between the 2 tests. When combined with physician assessment, OVERA correctly identified 75% of the malignancies missed by physician assessment alone. The overall validation for OVERA has not been as rigorous as that for OVA1. In addition, data is lacking to support change in outcomes and impact on management decisions. The OVA1 is specifically recommended by NCCN for assessment of patients who should undergo surgery by an experienced gynecologic oncologist and who can have surgery in the community; OVERA is not. The SGO and ACOG make more generalized statements of the utility of serum biomarker panels in this clinical scenario which cannot be interpreted as endorsement of OVERA in this clinical scenario.

Tests without medical necessity indications

The following tests do not have medical necessity indications:

- BBDrisk
- Chemo-FX
- Overa
- Prostate Risk Cancer Panel
- Risk of Malignancy Algorithm (ROMA)
- VeriStrat

Rationale

BBD[9-44]

Benign breast disease, commonly discovered during breast cancer screening, represents a spectrum of disorders ranging from benign non-proliferative disease (simple breast cyst, papillary apocrine change, mild hyperplasia of usual type) to atypical hyperplasia which confers an increased risk of developing breast cancer. The Gail model is the most commonly utilized risk assessment tool to assess breast cancer risk in patients who have never had a diagnosis of

breast cancer, ductal carcinoma in situ (DCIS), or lobular carcinoma in situ (LCIS). The sensitivity of the Gail model to identify women who will develop breast cancer is relatively low (28% to 44%), using a five-year risk of 1.67% as the cut point between "high" and "low" risk. The specificity of the Gail model is also modest, reported as 66%-88%. Other modalities for assessing risk of breast cancer are needed to predict the risk of developing breast cancer in this heterogenic population. The BBDRisk Dx is an immunohistochemistry assay of 4 cancer markers (MMP1, CEACAM6, HYAL1, and HEC1) developed to assess the level of risk for developing breast cancer in women with atypical or usual hyperplasias, sclerosing adenosis, and papillomas. The Cancer Risk Score ranges from 0-10 with higher scores corresponding to higher risk of subsequent cancer development.

- Low Risk < 0.5
- Intermediate Risk > 0.5 and ≤ 5.4
- High Risk > 5.4

Data is insufficient to support use of the BBDRisk Dx for risk-stratifying women with benign breast disease. Our search found no articles that met our pre-defined search criteria. Four articles from the manufacturer's website were evaluated. Three of these were retrospective publications based on banked tissue that identified MMP-1, CEACAM6, and HYAL 1 as candidate markers for identification of breast lesions that can develop into cancer. In a validation trial of archived hyperplastic breast tissue (149 atypical and 291nonatypical hyperplasia) in which clinical follow-up was available and patients had received no preventative treatments, the authors report that the average cancer rates in the first 5 years among low- and intermediate-risk groups were 2% and 15%, respectively. Among high-risk group, the average cancer rates at 5 years were 73% and 34% for atypical and nonatypical subjects, respectively. No prospective in-human trials are available. The BBDRisk Dx is not endorsed by medical specialty societies.

Chemo-Fx[29, 45-52]

Ovarian cancer is the fourth most common cause of cancer-related death in the U.S. In 2020, 21,750 new cases will be diagnoses and 33,940 people will die of this disease. Across multiple tumor types, the use of cytotoxic chemotherapies have been enhanced by use of biomarkers and gene testing. In the early 1990's and 2000's, in vitro chemosensitivity and resistance assays (CSRA) were developed to "personalize" chemotherapy treatment. Although CSRA have been studied in many tumor types, the most widely published data is in ovarian cancer. In vitro chemosensitivity and resistance assays such as the Chemo-FX assay or the extreme drug resistance (EDR) assay are laboratory tests that have been developed as a method to select the optimal chemotherapy regimen (sensitivity assays) or identify those agents least likely to be effective (resistance assays). ChemoFx is a cell culture-based chemoresponse assay that measures the sensitivity of tumor-derived malignant epithelial cells to chemotherapeutic agents in vitro, using quantification of cellular DNA as the assay endpoint.

In a 2014 systematic review to update recent medical literature for use of CSRA in the setting of ovarian cancer, the authors identified 3 primary analytical and clinical validation cohort studies and one prospective trial. In a retrospective trial, Gallion et al reported that in 135 cases with an exact match of CSRA to drug delivered, the hazard ratio for progression of the resistant group was 2.9 (95% CI, 1.4-6.3; P < 0.01) compared to the sensitive group and 1.7 (95% CI, 1.2-2.5) for the intermediate compared to the sensitive group. The median progression-free interval for patients treated with drugs assayed as resistant was 9 months, and 14 months for those with drugs assayed as intermediately sensitive. A statistically significant correlation was also seen in patients with partial and full match CSRA to drug received. Herzog et al. subsequently reported an association between assay response and overall survival in 192 patients with advanced EOC following first-line platinum-based chemotherapy with median overall survival of 72.5, 48.6, and 28.2 months for patients who were treated with agents reported as sensitive, intermediate, and resistant, respectively (HR = 0.7, 95% CI, 0.50-0.97, P = .03). Finally, Krivak et al in an observational study of 276 women with FIGO stage III-IV EOC cancer treated with first-line carboplatin-/paclitaxel-based therapy and assay-resistant for carboplatin reported an decrease in progression-free survival (11.8 vs 16.6 months compared to assay-intermediate and assay-sensitive patients (HR = 1.87, 95% CI, 1.29-2.70, P = .0009). In the lone prospective trial, patients (n=262) with persistent or recurrent epithelial ovarian cancer were empirically treated with one of 15 therapies, classified by the assay as: sensitive, intermediate, or resistant. Patients treated with an assay-sensitive regimen demonstrated significantly improved progression-free survival and overall survival while there was no difference in clinical outcomes between intermediate and resistant groups. Median progression-free survival was 8.8 months for sensitive vs 5.9 months for intermediate and resistant (hazard ratio [HR] = 0.67, P = .009). Response predicted by the CSRA was seen regardless of platinum-sensitivity or other covariates in multivariate analysis (HR = 0.66, P = .020). A statistically significant 14-month improvement in mean overall survival (37.5 months for sensitive vs 23.9 months for intermediate and resistant, HR = 0.61, P = .010) was demonstrated. This trial however is limited by its small sample size as well as does not take into consideration newer treatment options on market (e.g. PARPs and anti-angiogenic agent). Both NCCN and ASCO does not recommend the use of CSRAs for selection of chemotherapy in patients with ovarian cancer.

Prostate Cancer Risk Panel[4, 53-56]

Prostate cancer is the most common cause of malignancy in men in the United States. In 2020, 191,000 new cases will be diagnoses and 33,000 people will die of this disease. Multiple randomized trials provides evidence suggesting that screening does confer a small absolute benefit for reducing prostate cancer mortality and the risk of developing metastatic disease. Unfortunately, screening can often times result in false positives as well as over diagnosis of otherwise clinically indolent prostate cancer. Both imaging (e.g. multiparametric MRI) and specialty lab testing (e.g. 4KScore Test, prostate health index PHI, PCA3 assay, and Prostate Cancer Risk Panel) have been utilized for risk-

stratification of prostate cancer patients to determine when more invasive procedures are appropriate. The Prostate Cancer Risk Panel is a FISH analysis of 4 genes (ASAP1, HDAC9, CHD1, and PTEN) and incorporation into an algorithm of the biopsy specimen to determine the probability of higher tumor grade.

There is insufficient data to support the use of Prostate Cancer Risk Panel for risk assessment of high-grade prostate cancer. Our literature search uncovered no systematic review and meta-analyses and only one study to assess whether chromosomal rearrangements (CRs) can distinguish between low risk of progression (LRP) and intermediate/high risk of progression (IHRP) in prostate cancer. The authors evaluated 154 frozen which yielded 6 potential markers that were more frequently detected in high grade prostate cancer. Five of those were cross-validated in an independent sample set with statistically significant areas under the receiver operating characteristic curves (AUCs) (P < .01). Probes detecting deletions in PTEN and CHD1 had AUCs of 0.87 (95% CI, 0.77-0.97) and 0.73 (95% CI, 0.60-0.86), respectively, and probes detecting gains in ASAP1, MYC, and HDAC9 had AUCs of 0.71 (95% CI, 0.59-0.84), 0.82 (95% CI, 0.71-0.93), and 0.77 (95% CI, 0.66-0.89), respectively. There are no prospective human trial or outcome data available. Both NCCN and ASCO do not recommend Prostate Cancer Risk Panel for risk assessment of high-grade prostate cancer.

ROMA[26, 27, 29, 53-63]

Adnexal masses, most commonly found in the ovaries and fallopian tubes are a common gynecological problem effecting 5%-10% of all women in the US. The differential diagnosis is broad and may include benign causes (related to the menstrual cycle and hormonal to stimulation), cysts, acute causes (ectopic pregnancy, rupture, or infection), and neoplastic etiologies. The cornerstone of evaluation is a history and physical as well as imaging studies. In the work-up for malignancy, serum biomarkers may contribute to the evaluation although utility is limited. Biomarkers that have been marketed as a tool to help differentiate benign from malignant causes of adnexal masses include OVA1, OVERA, and the Risk of Malignancy Algorithm. The Risk of Malignancy Algorithm (ROMA) is a qualitative serum test (CA 125 and HE4) to further assess the likelihood of malignancy in women who are planning to have surgery for an adnexal mass. ROMA interprets the results using two separate logistic regression algorithms based on menopausal status from a score of 0-10.

- Premenopausal women: High risk of malignancy ≥ 1.31
- Postmenopausal women: High risk of malignancy ≥ 2.77

Screening

Data is insufficient to support use of ROMA as a screening exam. Both multicenter prospective study used to prompt FDA approval included ONLY women with an adnexal mass and scheduled to have surgery. Use of ROMA as a screening exam is not recommended by the FDA, SGO, or ACOG.

ROMA in women with adnexal mass and planned surgery

Evidence supporting the use of ROMA in women with adnexal mass and planned surgery is mixed. In a 2014 systematic review and meta-analysis to evaluate the diagnostic accuracy of CA125, HE4, and the Risk of Ovarian Malignancy Algorithm in the diagnosis of ovarian cancer, the author identified 32 articles that included 2,765 ovarian cancer cases and 4,875 benign gynecologic diseases for which HE4 and CA125 analyses were performed (from 28 studies) as well as 1,862 cancer cases and 4,077 benign diseases for which ROMA analysis was performed (from 19 studies). The three tests yielded similar discriminatory performances in the ovarian cancer diagnosis (AUC = 0.89; 95% CI, 0.86-0.92 for HE4, AUC = 0.87; 95% CI, 0.84-0.90 for CA125, AUC = 0.91; 95% CI, 0.88–0.93 for ROMA). Overall, HE4 yielded a higher specificity than CA125 and ROMA (HE4 93.60 [90.00–95.90] >CA125 82.10 [76.60–86.50] and ROMA 82.40 [77.40–86.50]), especially in the premenopausal subgroup (HE4 93.80 [88.40–96.80] >CA125 76.30 [63.30–85.70] and ROMA 85.10 [80.40–88.80]). In contrast, CA125 and ROMA performed significantly better in the postmenopausal subgroup than in the premenopausal subgroup (AUC [95 % CI]—CA125-premenopausal 0.85 [0.82–0.88] < post0.92 [0.89–0.94]; ROMA-premenopausal 0.86 [0.83–0.89] < post 0.93 [0.90–0.95]). In a more recent systematic review and meta-analysis, Chinese researchers reported the pooled estimates for the ROMA index including: sensitivity (0.90 [95% CI, 0.88-0.93]), specificity: (0.91 [95% CI, 0.89-0.94]), positive predictive value (0.90 [95% CI, 0.88-0.95]), negative predictive value (0.93 [95% CI, 0.91-0.95]), and area under ROC curve (0.96) compared to 0.71 (95% CI, 0.56-0.82), 0.87 (95% CI, 0.80-0.92), 0.82 (95% CI, 0.78-0.86), 0.92 (95% CI, 0.90-0.94), and 0.88 for HE4, respectively.

Key methodological shortcomings of the paper include the lack of comparison to CA125 as well as a predominately Asian population used in the review and analysis. In a recent 2019 systematic review and meta-analysis, the authors reported that ROMA and RMI-I have similar diagnostic performance for detecting ovarian cancer in women presenting with an adnexal mass. ROMA and RMI-I had a similar diagnostic performance in postmenopausal women (pooled sensitivity [87% vs 77%] and specificity [75% vs 85%], respectively, P = .29). In premenopausal women, RMI-I showed better specificity than ROMA (89% vs 78%, P = .022) with similar sensitivity (73% vs 80%, P = .27). Multiple prospective trials on the use of ROMA for the evaluation of adnexal mass and diagnosis of ovarian cancer have produced mixed results. Multiple subspecialty medical societies including NCCN, ACOG, and SGO does not recommend ROMA for evaluation of patients with adnexal mass and planned surgery.

Veristrat[44, 64-73]

Lung cancer is the second most prevalent cancer in the United States of both men and women; yet, lung is still the cause of more deaths than breast, prostate, colorectal, and brain cancers combined. In 2020, it is estimated that

230,000 patients will be diagnosed with lung cancer, and over 135,000 will die of this disease. A number of prognostic and predictive indicators are used to predict patient outcomes, including staging, clinical parameters (performance status, ethnicity), histopathology, tumor genotype, and PET imaging. VeriStrat is a blood-based proteomic test that is intended as a prognostic tool for predicting survival for standard therapies used in the treatment of NSCLC, as well as a predictive tool for response to EGFR TKIs. The VeriStrat assay uses an 8-peak proteomic signature to measures acute phase proteins and the acute phase response which indicates chronic inflammation and more aggressive cancer. Results are reported as either VeriStrat good or poor: VeriStrat Good results indicate a disease state that is more likely to respond to standard of care treatment while VeriStrat Poor results indicate a population that may be bettered served with clinical trials, novel combinations of therapies, genomic profiling, or earlier initiation of therapy.

In a 2014 meta-analysis that included 706 patients from seven studies, VeriStrat status (good versus poor) was able to shown to accurately predict clinical outcome in nonsmall cell lung cancer patients treated with tyrosine kinase inhibitors. The pooled HR for overall survival (95% CI, 0.32 to 0.49; P = .001) and progression free survival 0.49 (95% CI, 0.39 to 0.60; P < .001) both significantly favored the Veristrat good groups. Limitations of the meta-analysis included only univariate effect sizes were used to synthesize data due to the absence of multivariate effect sizes and unified clinical parameters in most of the included studies. Additional prospective trials have largely supported the prognostic accuracy to define poor and good risk patients. In the TOPICAL trial, VeriStrat was not a predictive marker for survival when considering first-line erlotinib for patients with NSCLC who had poor PS and were not recommended for platinum doublet therapies. However, VeriStrat was an independent prognostic marker of survival (HR was 0.54, (P < .001). The authors of BR.21 trial reported that VeriStrat was also a good prognostic marker for overall survival in both erlotinib-treated patients and those on placebo, independent of clinical covariates in the second line plus setting. VeriStrat was also predictive for objective response (P = .002), but was not able to predict for differential survival benefit from erlotinib (interaction P = .48). Similar results were found for progression-free survival. A follow-up study reported a 40% of change in treatment based on VeriStrat. Both trials did not stratifying for EGFR mutations which would not be congruent with current practice standards. In the biomarker-stratified, randomized phase 3 PROPOSE trial, patients classified as likely to have a poor outcome had better outcomes on chemotherapy as opposed to erlotinib (hazard ratio 1.72 [95% CI, 1.08-2.74], P = .022) in the second plus line setting. There was no significant difference in OVERAll survival between treatments for patients with a proteomic test classification of good (adjusted HR 1.06 [95% CI, 0.77-1.46], P = .714). Additional prospective and retrospective trials confirm the use of VeriStrat as a prognostic tool. As a whole, the literature does not address the use of newer generation TKIs, therapies directed at other genomic abnormalities (e.g. NTRK, RET, MET), nor chemo-immunotherapy. The use of VeriStrat also has not been shown to improve outcomes. Although there is some data to show that treatment may be altered, the reports are older and does not represent treatment current standard of care. Veristrat if not currently recommended by the NCCN (or major subspecialty medical society). Previous recommendation from the NCCN (2015) for the use of proteomic testing in advanced NSCLC was removed.

Non oncologic lab testing

Tests without medical necessity indications

The following tests do not have medical necessity indications:

- ActiTest
- BloodChip ID
- FibroSure / Fibrotest for any indication (HCV, ASH, NASH)

Rationale

Laboratory assessment of liver fibrosis (ActiTest, Fibrosure, Fibrotest)[74, 75 76-83]

Liver fibrosis occurs as a physiologic response to hepatocellular damage from a variety of etiologies, most commonly hepatitis B, C, alcohol use, and steatoheaptitis. The attempt to repair and replace damaged cells results in scarring and fibrosis due to the excessive accumulation of extracellular matrix proteins such as collagen.[76] Fibrosis is usually asymptomatic in the early stage but when it becomes severe, nodules of regenerating hepatocytes lead to cirrhosis and hepatocellular dysfunction.

The assessment of liver fibrosis represents a critical component in the evaluation of chronic liver disorders. Liver biopsy represents the gold standard diagnostic tool for liver fibrosis assessment, although noninvasive techniques are commonly used as a surrogate to the liver biopsy. Non invasive techniques may be less prone to sampling error and do not carry the small but potentially significant risks associated with liver biopsy including severe bleeding and/or pain and mortality.

There are several lab tests that use proprietary algorithms in combination with serum biomarkers to provide a non invasive measure of hepatic fibrosis.

- HCV FibroSURE /(FibroTest) and the FibroTest-ActiTest uses a combination of six serum hepatocellular biomarkers (α2-macroglobulin, haptoglobin, bilirubin, γ-glutamyl transpeptidase (GGT), apolipoprotein AI, and Alanine Aminotransferase (ALT)) plus age and sex in a proprietary algorithm to measure of fibrosis in patients with

HCV related liver disease. The FibroTest combines the first five biomarkers to measure the degree of hepatic fibrosis and generates a score ranging from F0 (none) to F4 (severe). The ActiTest uses ALT in combination with the other five hepatic biomarkers to assess hepatic inflammatory activity and generates a score ranging from A0 (no activity) to A3 (severe activity).

- ASH FibroSURE/(ASH Test) uses a combination of 10 serum hepatocellular biomarkers (α2-macroglobulin, haptoglobin, apolipoprotein AI, bilirubin, GGT, ALT, AST, total cholesterol, triglycerides, and fasting glucose) of liver function together with age, sex, height, and weight in a proprietary algorithm to measure the risk of fibrosis in patients with Alcoholic liver disease
- NASH FibroSURE /NASH FibroSURE (NASH Test) uses combination of 10 of serum hepatocellular biomarkers (α2-macroglobulin, haptoglobin, apolipoprotein AI, bilirubin, GGT, ALT, AST, total cholesterol, triglycerides, and fasting glucose) in combination with age, sex, height, and weight to measure the risk of fibrosis in patients with non alcoholic steatohepatitis

In addition, the Fib-4 and APRI tests make use of a non proprietary algorithm and widely available serum biomarkers (AST, platelet count, and/or ALT). Ultrasound and magnetic resonance elastography are other non invasive methods for assessing liver fibrosis.

The American Gastroenterological Society[84] makes a strong recommendation based on moderate quality evidence for the use of vibration controlled transient elastography (VCTE) instrad of serum tests in the assessment of HCV cirrhosis. Other high quality evidence based guidelines[78] recommend use of non invasive testing with elastography or serum biomerks as an alternative to liver biopsy, but do not recommend use of proprietary alternatives over more widely available tests.

The clinical validity of Fibrosure/Fibrotest has been the subject of several systematic reviews and there is no evidence that proprietary serum biomarkers offer superior clinical validity to elastogrpahy or non proprietary serum alternatives. A 2014 systematic review comparing Fibrotest to elastography found no difference in diagnostic accuracy between the tests.**[77]** Another 2014 systematic review assessed the diagnostic accuracy of cirrhosis in patients with Hepatitis B. Based on six studies of moderate quality, the summary sensitivities and specificities of the FIB-4 were 44.7% (95% CI, 39.4%-50.2%) and 86.6% (95% CI, 84.3%-88.7%) with an overall diagnostic accuracy ranging from 74% to 93%. The same review identified 9 studies of overall lower quality using the FibroTest and found an overall diagnostic accuracy ranging from .68 to .92 with significant heterogeneity limiting the pooled assessment of accuracy. The authors concluded that while “Fibrotest has excellent diagnostic accuracy... FIB-4, a relatively moderate marker, has better summary diagnostic accuracy and could be measured and calculated relatively easily”.[85] A more recent systematic review in NAFLD found that elastography was slightly more accurate than Fib-4 with an estimated diagnostic accuracy of > 95% compared to 84%.[83] Other reviews similarly find no evidence for superior performance of the fibrotest in all cirrhotic patients when compared to fib-4 or elastography.**[80]**

No studies assessing the clinical utility of Fibrotest/FibroSure and/or the ActiTest were identified.

BloodChip ID[2, 88-9]

The safe and rationale use of blood transfusons is an essential medical intervention to prevent and manage disease. Safety during the transfusion process depends on both the integrity of the blood products and the clinical transfusion process.[86] A variety of adverse effects can complicate the transfusion process including acute hemolytic reactions, nonhemolytic febrile transfusion reaction, allergic reactions, alloimmunzartion, transfusion related acute lung injury (TRALI), and autoimmune hemolytic anemia.[87] Compatibility testing and blood typing are important to reduce transfusion risks. Blood typing assesses for the presence or absence of antigens on the erythrocyte cell surface that risk promoting an antibody response in the recipient. There are now 35 blood groups systems compromising more than 300 antigens.[88] Blood is routinely typed for ABO and Rh(D), but not for minor antigens.[89] However, if antibodies to a minor antigen are present in a recipients serum donated blood must lack the relevant antigen(s). In patients at risk of having multiple antibodies, red blood cell (RBC) phenotyping can identify which antibodies a the patient is capable of making. Such phenotyping is usually performed using specific antisera via hemagglutination.[89] Standard methods however can be limited in recently transfused patients, is labor intensive and may not always be possible. In these situations, molecular typing can identify antigen negative donors as most clinically significant antigens are single nucleotide polymorphisms (SNPs) which closely correlate to the RBC phenotype.

Human platelet antigens (HPA) are SNPs on platelet antigens responsible for immune mediate platelet disorders, such as neonatal autoimmune thrombocytopenia (NAT), post transfusion purpura (PTP) and multi platelet transfusion refractoriness (MPTR). While 27 HPA systems have been identified, HPA 1-6, 9, and 15 are primarily responsible for disease.[90, 91] Options for testing include platelet antibody/ antigen tests and platelet genotyping.

The BloodChip ID is a high throughput blood genotyping microarray platform based on Luminex R xMAP technology for simultaneous determination of 37 red blood cell (RBC) antigens (ID CORE XT) and 18 human platelet antigens (HPA) (ID HPA XT) using the BIDS XT software.[2] It is one of a variety of technologies for genotyping which also include Beadchip, Genome Lab and Open Array.[88] There is limited peer reviewed literature on the system. For clinical validity, there is low quality evidence that BloodChip has comparable clinical and analytic validity to other molecular genotyping technologies. In the lagest retrospective study to date, an analysis of 500 samples found a comparable diagnostic

accuracy to current systems with a faster processing time.[2] There is no evidence for the added clinical utility offered by the Blood Chip ID product relative to standard of care technologies.

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Codes

The following code list is not meant to be all-inclusive. Authorization requirements will vary by health plan. Please consult the applicable health plan for guidance on specific procedure codes.

Specific CPT codes for services should be used when available. Non-specific or not otherwise classified codes may be subject to additional documentation requirements and review.

CPT

81500	Onco (ovarian) biochemical assay two proteins
81503	Onco (ovarian) biochemical assay five proteins
81535	Oncology gyne live tum cell cltr&chemo resp 1st
81536	Oncology gyne live tum cell cltr&chemo resp add
81538	Oncology lung ms 8-protein signature
81539	Oncology prostate biochemical assay 4 proteins
81596	NFCT DS CHRNC HCV 6 BIOCHEM ASSAY SRM ALG LVR
0002M	Liver dis 10 assays serum algorithm w/ASH
0003M	Liver dis 10 assays serum algorithm w/NASH
0053U	ONC PRST8 CA FISH ALYS 4 GENES NDL BX SPEC ALG
0067U	ONC BRST IMHCHEM PRTN XPRS PRFL 4 BMRK CA PRTN
0084U	RBC DNA GNOTYP 10 BLD GRP PHNT PREDICT 37 RBC AG

HCPCS

None

ICD-10 Diagnosis

Refer to the ICD-10 CM manual

History

Status	Review Date	Effective Date	Action
Created	07/08/2020	01/01/2021	Original effective date.