Alpha-Fetoprotein

The use of prenatal serum alpha-fetoprotein (AFP) determinations to monitor fetal abnormalities has become accepted practice since 1986 when the American College of Obstetrics and Gynecology recommended its use to detect the presence of open neural tube defects (NTD) in developing fetuses [1]. Since then, the use of AFP measurements has been extended to the detection of chromosomal anomalies, principally trisomy 21 (Down syndrome) [2] and trisomy 18 [3]. Although the original investigations into the prenatal detection of Down syndrome relied solely on AFP results, more recent studies have shown an improvement in detection when measurements of unconjugated estriol (uE3) and human chorionic gonadotropin (hCG) are combined with AFP [4,5]. In order to permit comparison of test results between testing centers, all values are expressed as multiples of the median (MoM) for the gestational age of the fetus.

CORRECTION OF MoM RESULTS

MoM values for AFP, hCG, and uE3 are affected by the weight of the mother and twin gestations. Each of these MoMs is corrected for maternal weight. Correction is not made for twins. The AFP MoM is also affected by insulin dependent diabetes mellitus and race. Corrections for these factors are made when the information is available.

NEURAL TUBE DEFECTS

The incidence of NTD in the white race is 6 in 10,000, while in the black race it is only 3 in 10,000. Insulin dependent diabetics have an *a priori* risk of 35 in 10,000. Patient-specific risks are calculated from the corrected AFP MoM and the *a priori* risk. When the AFP MoM is greater than 2.5, 75% of open spina bifida and 79% of ventral wall defects will be detected [6].

CHROMOSOMAL ANOMALIES

Trisomy 21 has been associated with low AFP MoM values, less than 0.5. Using a combination of age (≥35 years) and AFP MoM, approximately 35% of Down syndrome affected fetuses can be detected *in utero* [4]. When uE3 and hCG MoMs are added to the risk assessment, the detection is increased to 58% [4,5]. Additionally, the rarer trisomy 18 anomaly may also be identified. Approximately 85% of trisomy 18 will be identified by triple marker screening when all of the following are present: the combination of AFP MoM is less than 0.75, the uE3 MoM is less than 0.60, and the hCG MoM is less than 0.55 [3].

RISK CALCULATIONS

When the gestational age of the fetus is 15 weeks or less, a patient specific risk for NTD cannot be calculated. Only the corrected MoM is reported. For gestational age less than 16 weeks or greater than 20 weeks, maternal serum AFP monitoring is not recommended. Maternal serum AFP testing should be done between 16-20 weeks of gestation. Genetic counseling is recommended for all patients whose age at EDC is 35 years or older. No *a priori* data exist for Down syndrome when the maternal age is less than 17 or greater than 49. For risk calculations in patients of these ages, *a priori* risks for 17 or 49 years are used.

References:
1. Prenatal Detection of Neural Tube Defects. American College of Obstetrics and Gynecology Technical Bulletin 1986;99:1-6.
2. Palomaki GE, Haddow JE. Maternal serum alpha-fetoprotein, age, and Down syndrome risk. Am J Obstet Gynecol 1987;156:460-3
3. Palomaki GE, Knight GJ, Haddow JE, Canick JA, Saller DN, Panizza DS. Prospective intervention trial of a screening protocol to identify fetal trisomy 18 using maternal serum alpha-fetoprotein, unconjugated oestriol, and human chorionic gonadotropin. Prenatal Diag1992;12:925-30.
4. Haddow JE, Palomaki GE, Knight GJ, Williams J, Pulkkinen A, Canick JA, Saller DN, Bowers GB. Prenatal screening for Down's(sic) syndrome with use of maternal serum markers. N Engl J Med 1992;327:588-93.
5. Phillips OP, Elias S, Shulman LP, Andersen RN, Morgan CD, Simpson JL. Maternal serum screening for fetal Down syndrome in women less than 35 years of age using alpha-fetoprotein, hCG, and unconjugated estriol: A prospective 2-year study. Obstet Gynecol 1992;80:353-8.
6. Adams MJ, Windham GC, James LM, Greenberg F, Clayton-Hopkins JA, Reimer CB, Oakley GP. Clinical interpretation of maternal serum "-fetoprotein concentrations. Am J Obstet Gynecol 1984;148:241-54

Glycosylated Hemoglobin

Glycohemoglobin is formed from Hemoglobin A by non-enzymatic addition of carbohydrate to N-terminal amino groups of hemoglobin polypeptide subunits. The conversion takes place within the erythrocytes at a rate that is proportional to the erythrocytic concentration of glucose. Several forms of glycohemoglobin are formed; HbA_{1a}, HbA_{1b}, and HbA_{1c}. As a sum, these are reported as "fast" or total glycohemoglobins. Of these, one species, HbA_{1c}, has been considered to more closely parallel the previous history of glucosemia.

Because of the shortened lifespan of erythrocytes in patients with hemolytic anemia, HbA_{1c} results will be lower than expected. The magnitude of the effect will depend upon the severity of the anemia. Conditions such as polycythemia or splenectomy which cause increased red cell lifespan may be associated with increased HbA_{1c} results.

Human Immunodeficiency Virus

Antibody Testing

The Human Immunodeficiency Virus (HIV) is classified in the family Retroviridae. Antibodies to the HIV virus have been found in patients with AIDS, pre-AIDS, and from healthy individuals at risk for AIDS. Detection of HIV antibody utilizes enzyme-linked immunosorbent assay (ELISA) technology.

The primary use of the HIV antibody test is to screen and restrict antibody positive donors from donating blood and blood components. A positive result for HIV antibody is not, by itself, diagnostic of AIDS.

The following table lists the laboratory tests frequently used to gain more information about possible HIV infections.

TEST	UNINFECTED PATIENT RESULTS	HIV INFECTED PATIENT RESULTS
Western Blot	Negative	Positive
Anergy Panel	Adequate cell-mediated immunity	Defective cell-mediated immunity
T-cell helper to suppressor ratio (T4/T8)	Normal (2.0)	Decreased (<0.6) T4 decreased T8 normal or increased
White Cell Count	Normal (4.0-11.0)	Absolute number normal to decreased
Differential of WBC	Normal	Lymphocytes normal to increased
HIV-1 DNA by PCR	Not Detected	Detected

Other laboratory results that may be helpful in HIV infections:

- Positive cultures or serological tests for antibody (percentage of positive will depend on patient's risk group).
    - Cytomegalovirus Antigen
    - Epstein-Barr Virus Antibody
    - Gonorrhea Culture
    - Hepatitis A Antibody
    - Hepatitis B Antigens and Antibodies
    - Herpes Antigen
    - Syphilis Antibody

Quantitative Immunoglobulins listed in the table below:

TEST	AIDS	HEALTHY HETERO-SEXUAL RESULTS	HEALTHY HOMO-SEXUAL RESULTS
IgA	Increased 2 fold	Normal	Normal
IgD	Increased 10 fold	Normal	Increased 3 fold
IgG	Normal to small increase	Normal	Normal to small increase
IgM	Normal to small increase	Normal	Normal

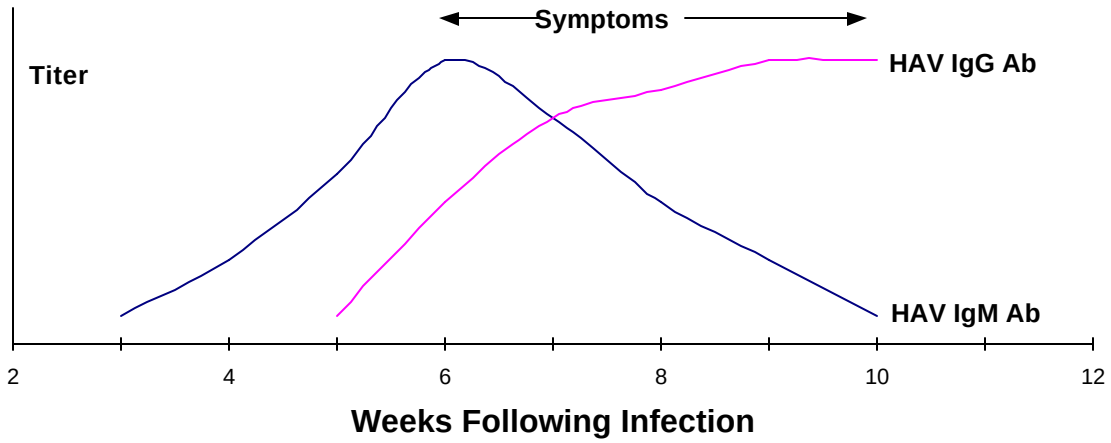
Hepatitis Testing

There are three main classes of viral hepatitis infection: hepatitis A, hepatitis B, and hepatitis C. Although clinically similar, these forms of viral hepatitis differ epidemiologically, immunologically, and in prognosis.

HEPATITIS A (HAV)

Hepatitis A is caused by an RNA virus with an incubation period of 15-50 days. Transmission is by personal contact, contact with contaminated oral or fecal material, contaminated drinking water, or raw mollusks. Rarely contact is made through contaminated milk, orange juice, or percutaneous transmission. Eighty-five to ninety-five percent of HAV patients are between the age of 1-15. The majority of the remaining cases are between the ages of 15-34. HAV does not develop into a chronic or carrier state.

Hepatitis A Immune Response



To determine recent exposure:

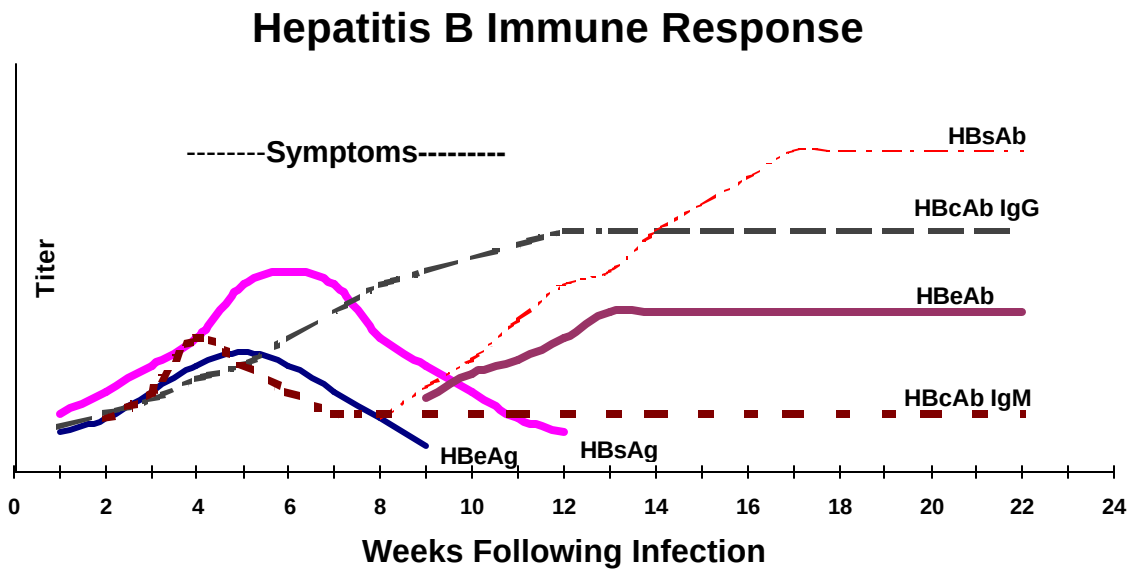
- Anti Hepatitis A (IgM)
- Test acute and convalescent serum samples.

To determine past exposure, may last for life:

- Anti Hepatitis A (polyvalent)
- Test acute and convalescent serum samples.

HEPATITIS B (HBV)

Hepatitis B is caused by a DNA virus with an incubation period of 6 to 16 weeks. Patients with HBV are infectious 4-8 weeks before symptoms and until HBsAg is no longer detectable. Five to ten percent of new infections develop into a carrier state; HBV is a significant cause of chronic active hepatitis. Because 5-10% of infected patients become carriers, a single reactive test may not be enough to indicate an acute infection. Repeat HBsAg testing along with other tests may be needed to determine acute or carrier status.



To determine past exposure (or vaccination) and immunity:

- Hepatitis B surface antibody (HBsAb)

To diagnose current infection:

- Hepatitis B surface antigen (HBsAg); preferred test #1
- Hepatitis B core antibody IgM (HBcAb-IgM); preferred test #2
- Hepatitis B e antigen (HBeAg); supportive evidence

To determine convalescence, with minimal chance of becoming a chronic carrier:

- Hepatitis B surface antibody (HBsAb); preferred test
- Hepatitis B e antibody (HBeAb); supportive evidence
- Polyvalent HBcAb; supportive evidence
- Detection of HBsAb in the absence of positive HBsAg or HBeAg tests, indicates probable convalescence.

To diagnose a chronic infection:

- Hepatitis B surface antigen (HBsAg)
- Hepatitis B surface antibody (HBsAb)
- Persistence of HBsAg and lack of HBsAb indicate the carrier state.

TEST RESULTS AT DIFFERENT STAGES OF HEPATITIS B INFECTION

A "+" indicates the probability that the result will be positive.

HBcAb	HbsAg	HBsA	HbeAg	HbeAb	HbcAb

IgM		b			IgG	Interpretation
-	-	-	-	-	-	No evidence of hepatitis B infection
+/-	+	-	+	-	-	Subclinical or acute hepatitis
+	+	-	+	-	+	Chronic infectious hepatitis
+	+	-	-	+	+	Chronic or early convalescent hepatitis
+	-	+	-	-	+	Convalescence, recovery
+/-	-	+	-	-	+	Recovery or following active immunization
-	-	-	-	-	+	Convalescence or low level carrier

HEPATITIS C (HCV)

Hepatitis C is caused by an RNA virus and is the predominant cause of non-A, non-B hepatitis (NANBH). Studies indicate that HCV is transmitted through contaminated blood and blood products, through blood transfusions or through close personal contacts. HCV can develop into a chronic or carrier state. Testing methods are currently available for screening-HCV ELISA (detects antibodies to three regions of the HCV genome (NS3, NS4 and Core) and for confirmation-HCV RIBA (detects antibodies to 5 recombinant antigens).

HEPATITIS, DELTA

- Antibody to delta antigen

HEPATITIS, NON-A, NON-B

- Hepatitis A IgM Antibody (HAAb-IgM)
- Hepatitis B surface antigen (HBsAg)
- Hepatitis B core IgM Antibody (HBcAb-IgM)
- Hepatitis C IgG Antibody (HCAb-IgG)

The absence of these 4 markers indicates probability of non-A, non-B hepatitis.

Anti-Thyroid Peroxidase Antibodies/ Anti-Thyroid Antibodies

Normal thyroid tissue expresses three principal antigens: TSH receptor, thyroglobulin and thyroid peroxidase. In autoimmune disorders affecting thyroid function, autoantibodies are produced against one or more of these three antigens.

According to the National Academy of Clinical Biochemistry Standards of laboratory Practice for the diagnosis and monitoring of thyroid disease, anti-thyroid peroxidase antibodies (anti-TPO Abs) have emerged as the most generally useful marker for auto-immune thyroid disease. These auto-antibodies were historically referred to as anti-microsomal antibodies. The major microsomal membrane component was subsequently identified as the thyroid peroxidase enzyme. This enzyme catalyzes iodination of tyrosine
residues within the thyroglobulin molecule in the biosynthetic pathway leading to the production of thyroid hormones.

In place of the less well-defined microsomal antigen used in hemagglutination assays, highly purified preparations of TPO antigen are used in today's immunoassays. Results for the new anti-TPO Abs are reported in terms of U/L instead of titers. The new assay removes the subjectivity inherent in agglutination assays.

The normal reference interval for TPO Ab assays remain controversial. When very sensitive methods are employed, TPO Abs are detected in healthy persons with normal thyroid function; the biological significance of low levels of TPO Abs is not clear. They may be normal variants, false positives, or reflect true underlying thyroid autoimmunity. Our method is quantitative and has a normal reference interval of less than 35 IU/mL. In a recent study comparing the quantitative anti-TPO results with the anti-microsomal antibody titer results, the concordance was 48 of 49 samples or 98%. The discordant sample had an anti-TPO result of 15 IU/mL repeatedly and an anti-microsomal antibody titer of 1:1600, repeatedly. The anti-microsomal antibody test probably represents a false positive result because of the possibility of cross-reaction with the anti-TG antibodies, if present in high concentrations.

In Hashimoto's thyroiditis, anti-TPO Abs are found in virtually all cases. Elevated levels are also found in 85% of Grave's disease.

The new anti-thyroglobulin is a quantitative test with a normal reference interval less than 40 IU/mL. In a recent study comparing the quantitative anti-TG results with the qualitative anti-TG titer results, the concordance was 100% in 34 samples.

Clinical Application of Serum Tumor Markers

Effective serum tumor marker tests would have the following characteristics:

- The marker is negative in health or benign disease.
- The marker is exclusively produced by specific tumor cells.
- The marker is present frequently in the targeted malignancy.

- The marker is detectable in occult disease.
- The marker's degree of expression reflects tumor burden and prognosis.
- The marker's degree of expression correlates with therapeutic results.

There are no currently available markers that have all six characteristics. However, many markers perform well by one or more characteristics and are clinically useful. No markers are currently useful as screening tools in asymptomatic persons.

Alpha-fetoprotein (AFP)

AFP has been used to screen for hepatocellular carcinoma in patients with liver disease, especially chronic type B hepatitis. Small asymptomatic tumors are associated with AFP values greater than normal but less than 215 ng/mL. AFP has also been used for determining the prognosis and monitoring therapy in non-seminomatous testicular cancer.

$Beta_2$-Microglobulin

$Beta_2$-Microglobulin has been used to predict response to treatment for lymphoma. Patients with $Beta_2$-Microglobulin levels less than 3.0 mg/L have a higher remission rate than those with elevated $Beta_2$-Microglobulin.

CA 15-3

CA 15-3 is used as a marker of breast cancer. However, it is present in the serum of healthy men and women and is increased in benign and malignant diseases including cancer of the stomach, pancreas, bile duct, colon, thyroid, lung, cervix, endometrium, ovary, and breast. Serum CA 15-3 increases during progression of disease and declines with successful treatment. Sensitivity varies with disease stage, 0-36% in stages I and II and 11-100% in stages III and IV. Specificity is between 85-100%

CA 19-9

CA 19-9 is infrequently elevated in colorectal cancer (20%), gastric cancer (42%) and hepato cellular cancer (22-51%) but is frequently elevated in patients with pancreatic cancer (70-100%). Elevations also occur in patients with pancreatitis and liver disease. Elevations following surgical resections predict recurrent cancer.

CA 27.29

CA 27.29 is a marker for breast cancer and has been shown to detect an antigen similar, if not identical to CA 15-3. As breast cancer progresses, the level of CA 27.29 antigen in the blood increases. The FDA approved this test in 1996 for breast cancer recurrence. When the test was applied to 166 women who had previously had breast cancer, it detected 15 or 26 women who had a recurrence (sensitivity of 58%) and in 8 of 140 women who did not (specificity of 94%).

CA-125 II

CA-125 II has been used as marker for ovarian cancer. It has a sensitivity of 80% and a specificity of 99% in the general population. In women with pelvic masses, the sensitivity is 87% and the specificity is 88%. Elevation correlates with tumor size and stage. A rising level

during chemotherapy indicates progressive disease. However, normal values may be found in residual or recurrent disease.

Carcinoembryonic Antigen (CEA)

CEA has been widely accepted for colorectal carcinoma and for detecting recurrent cancer after surgery. CEA is also elevated in smokers.

The efficacy of CEA in detecting surgically curable recurrent colon cancer has been questioned. [Moertel CE et al, An evaluation of the carcinoembryonic antigen (CEA) test for monitoring patients with resected colon cancer. JAMA 93; 270: 943-7]

Prostatic Acid Phosphatase (PAP)

Although PAP is elevated in 85 to 95% with patients with metastatic prostate cancer, only 12-30% of patients with early stage cancer have elevated levels. Elevated PAP may also occur in other cancers including multiple myeloma, osteogenic sarcoma, and bone metastases from other non-prostatic cancers. It may also be elevated in non-malignant diseases such as osteoporosis, hyperparathyroidism, and hyperthyroidism as well as in benign prostatic hypertrophy.

Prostate Specific Antigen (PSA)

PSA is localized to prostate tissue and is elevated in men with benign or malignant prostate disease, precluding its use as a sole screening test. Patients with stage A or B prostatic cancer cannot be distinguished from patients with benign prostatic hypertrophy. After prostatectomy, PSA levels fall. Rising levels are associated with recurrent cancer in more than 90% of patients.

Free Prostate Specific Antigen (PSA II)

Men whose digital rectal examinations are not indicative of cancer but whose prostate-specific antigen (PSA) levels are in the range of 4 ng/mL to 10 ng/mL today find themselves in a diagnostic gray zone. About a quarter of them have prostatic carcinoma, usually in its earliest, most curable stage.

Determination of the free to total PSA ratio appears to show promise for increasing the specificity of a mildly elevated PSA result with minimal loss of sensitivity for prostate cancer. PSA in blood is predominantly (about 85 percent) bound to anti-chymotrypsin and other enzyme inhibitors with only a minority (about 15 percent) circulating in an unbound and probably enzymatically inactive form. For reasons not fully understood, patients with prostate cancer have a significantly lower percentage of free PSA than patients with benign prostatic hypertrophy.

Patients with free to total ratios of less than 7 percent have a high (greater than 90 percent) risk of prostate cancer which is altered little by their age or their exact level of total PSA. Conversely, patients with greater than 25 percent free PSA have a very low (less than 10 percent) risk of cancer, at least at PSA levels under 10 ng/mL.

HUMAN IMMUNODEFICIENCY VIRUS VIRAL LOAD TESTING

Quantitation of human immunodeficiency virus type 1 (HIV-1) loads in the plasma of infected patients is routinely used to determine the risk of disease progression and to assess the short

and long term response to therapy with antiretroviral drugs. The minimal decrease or increase in HIV-1 RNA copies/mL plasma indicating a favorable response to therapy or drug-resistance/disease progression, respectively, is a change in the result of at least 0.5 log (threefold). Changes of less than or equal to 0.5 log are likely to be due to the normal biological and laboratory test variation. When an infected patient is first tested, two baseline measurements, 2 to 4 weeks apart, should be made prior to initiation of therapy. For monitoring therapy, the patients can be tested 3 to 4 weeks after starting or changing therapy, every 4 weeks when making critical clinical decisions, and then every 3 to 4 months.

Because of the possibility of low-level false positive results, viral load testing should rarely if ever be used to establish a diagnosis of HIV infection. The enzyme-linked immunosorbent assay (ELISA) screen for HIV antibodies followed by Western blot confirmation provides a greater than 99% accuracy for the detection of HIV infections. The ELISA screen for HIV antibodies, however, may be negative during the primary infection for 3 to 4 weeks prior to seroconversion. During this window period following infection, initial viremia usually occurs within 4 to 11 days and the viral load reaches very high levels immediately prior to seroconversion. During the first 30 days after infection, the median HIV-1 RNA level has been found to be over 200,000 copies of the virus per mL of plasma and has ranged from a low of about 27,000 copies/mL to over 1,600,000 copies/mL. In contrast, false-positive HIV-1 viral load results from uninfected patients have been reported in the range of 5 to 150 copies/mL. Therefore, these false-positive results are considerably less than 10% of the lowest reported plasma viral load during the interval of seroconversion in the newly infected patients. False-positive HIV-1 RNA levels may occur at least 2 to 6% of the time when plasma samples from infected patients are tested.

Reference:

Hodinka, R.L. The clinical utility of viral quantitation using molecular methods. Clin. Diagn. Virol. 1998. **10**:25-47.

Human Papilloma Virus

The human papilloma virus (HPV) has been established as the primary cause of cervical cancer in nearly all cases.[1] Testing for HPV can help with triaging women with atypical squamous cells of undetermined significance (ASCUS). The test is also indicated for screening, in conjunction with the Pap test, of women over age 30 for HPV infection. The HPV DNA test does not test for cancer, but for the HPV viruses that can cause cell changes in the cervix. If left untreated, these changes can eventually lead to cancer in some women. The test should be used along with the Pap test, a complete medical history and an evaluation of other risk factors to help physicians determine what kind of follow-up is necessary.

The sensitivity of HPV DNA testing for the detection of biopsy-confirmed high grade squamous intraepithelial lesion (HSIL) in women with ASCUS is 83% to 100% and is higher than the sensitivity of a single repeat cervical cytological test in all of the reported series. The negative predictive value of DNA testing for high-risk types of HPV is generally reported to be 98% or greater.[2]

HPV are small DNA tumor viruses that belong to the family of Papovaviridae. There are 23 distinct HPV types which are specific to the genital tract of both males and females. Clinical manifestation of HPV infection is dependent upon epithelial location, HPV type and host immune status. Viral DNA of HPV type 16 and type 18 have been found in 60% and 20% of cervical carcinomas, respectively.[3] Historically, they are regarded as high-risk cancer associated HPVs. HPV types 31, 33, and 35 are more frequently detected in HSIL. These have demonstrated an intermediate cancer association. Additional HPV DNA types 45, 51, 52, 56, 58, 59, and 68 have been identified as the principal HPV's detectable in the remaining HSIL lesions and in low grade SIL.[4] Currently, high-risk HPV types refer to HPV 16/18/31/33/35/39/45/51/52/56/58/59/68.

References:

1. Walboomers JMM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol.* 1999; 189:12-19.
2. Wright TC, Cox JT, Massad LS, Twiggs LB, and Wilkinson EJ, 2001 Consensus Guidelines for the Management of Women With Cervical Cytological Abnormalities, JAMA, 2002(16); 287: 2120-2129.
3. Pfister H, The role of human papilloma virus in anogenital cancer. In Lorincz AT, Reid R, editor. Human papillomavirus 1. 2nd ed. Obstet Gynecol Clin NA 1996;23:579-595.
4. Lorincz AT, Reid R, Jenson, AB, Greenberg MD, Lancaster W, Kurman RJ, Human papillomavirus infection of the cervix: relative risk associations of 15 common anogenital types. Obstet Gynecol 79:328-337; 1992.

Whole Blood Lead, Lead Group(Lead, ZPP), and ZPP

Lead affects the central and peripheral nervous systems, the heme biosynthetic pathway, and the renal system. The clinical signs and symptoms of lead poisoning are nonspecific. Lead inhibits aminolevulinic acid dehydratase, necessary for the synthesis of heme from porphyrin. As a result, erythrocyte protoporphyrin levels are increased, and heme-deficient anemia may then ensue. Irritability, anorexia, malaise, headache, constipation, attacks of abdominal pain (lead colic), and renal toxicity are common symptoms of early toxicity. Therefore, a venous blood lead measurement is essential for diagnosis.[1, 2, 3] Whole blood lead levels lower than 10 µg/dL are considered normal in children by the CDC. The WHO has defined whole blood lead levels greater than 30 µg/dL in adults as indicative of significant exposure. Lead levels greater than 60 µg/dL require chelation therapy.

Zinc protoporphyrin (ZPP) is an indirect measure of iron availability in the developing erythroblast. Significant lead poisoning (lead levels greater than 25 µg/dL) raises ZPP concentrations as the result of inhibition of the ferrochelatase. Specimens collected for lead testing, particularly blood collected by finger sticks, are notoriously prone to contamination by exogenous lead; contamination should be suspected in specimens with elevated whole-blood lead levels that do not show concordance with zinc protoporphyrin (ZPP) measurements. In an occupation setting, the Occupational Safety and Health Administration currently requires both whole blood lead and ZPP testing. Erythrocyte protoporphyrin levels greater than 60 µg/dL are a significant indicator of lead exposure.[2] ZPP is not currently recommended by the CDC for lead screening in children 6 years of age and younger.

References:

1. Analytical Procedure For The Determination Of Lead In Blood And Urine; Approved Guideline, NCCLS, C40-A, V 21, No.9, 2001.
2. T. Moyer, Toxic Metals, Chapter 28, Tietz Textbook of Clinical Chemistry, 3rd edition, pp989 - 991, 1999.
3. M. Ottlinger, R. Zumwalde, R. Roscoe, M. Kosnett, K. Hipkins, R. Meister, and A Materna, Adult Blood Lead Testing, Clin. Lab. News, June 2002

Appendix A: Blood Lead in Children According to CDC Screening Young Children for Lead Poisoning Program (1997)

Result	Comment
0 - 9 µg/dL	No action unless exposure sources change.
10 -14 µg/dL	Consider at least one follow-up test within 3 months. Provide family lead education regarding preventive actions.
15 -19 µg/dL	Consider one follow-up test within 2 months. Provide family lead education. Refer for Social Services, if necessary. If blood levels (BLLs) persist (i.e., two venous BLLs in this range at least 3 months apart) or worsen, proceed according to actions for BLLs 20-44.
20 -44 µg/dL	Consider clinical management, environmental investigation, and lead-hazard control.
45 -69 µg/dL	Begin coordination of care (case management), clinical management, environmental investigation, and lead-hazard control.
≥ 70 µg/dL	This is a critical concentration. A second venous test, hospitalization, appropriate chelation therapy, and removal from lead exposure are urgently recommended.
Elevated results from non-certified lead-free tubes may be due to contamination. Elevated levels of blood lead should be confirmed with a second specimen collected in a metal-free tube.	

Appendix B: Blood Lead in Adults

Result	Comment
< 10 µg/dL	No action required unless exposure sources change.
10 - 24 µg/dL	Identify and minimize exposure.
25 - 49 µg/dL	Remove from exposure, if symptomatic.
50 -79 µg/dL	Remove from lead exposure. Immediate medical evaluation. Excessive chelation therapy is discouraged.
≥ 80 µg/dL	Chelation may be indicated if symptomatic. Seek consultation.
Note: Blood lead in adults, occupationally exposed: Refer to OSHA and/or industrial standards.	

Appendix C: Lead, Industrial Exposure Panel

Components	Reference Interval
Lead, Whole Blood	0-16 years: 0.0-9.9 µg/dL 16-150 years: 0.0-24.9 µg/dL

Zinc Protoporphyrin (ZPP), Whole Blood	0-69 µmol ZPP/mol heme
Zinc Protoporphyrin (ZPP), Whole Blood	0-40 µg/dL

Appendix D: Action Required for Workers with Elevated Lead Values (OSHA, Occupational Exposure to Lead, 1978)

Number of Tests	µg/dL	Action Required
1	≥ 40.0	Notification of workers in writing; medical examination of worker and consultation.
3	≥ 50.0	Removal of worker from job with potential lead exposure.
1	≥ 60.0	Removal of worker from job with potential lead exposure.
2	≤ 40.0	Reinstatement of worker in job with potential lead exposure is based upon symptoms and medical evaluation.

OSHA requirements in effect since 1978 call for the measurement of whole blood lead and zinc protoporphyrins (ZPP) (NCCLS document C42-A, November 1996) to evaluate the occupational exposure to lead. OSHA requires ZPP whole blood testing reported in units of µg/dL. Federal lead construction standards require worker to be notified and removed from the job at levels of 50 µg/dL and higher until physician authorizes return.

Intact Parathyroid Hormone (intact PTH)
PTH Panel and PTH Group

Intact parathyroid hormone (parathyrin, PTH), a single-chain polypeptide (with a molecular mass of approximately 9500 daltons) containing 84 amino acids, regulates the concentration of ionized calcium in extracellular fluids. The *in vivo* half-life of iPTH is 2 to 5 minutes.[3] Elevated PTH levels can be found in about 90% of the patients with primary hyperparathyroidism. Suppressed PTH levels can be found in about 95% of hypercalcemic patients associated with malignancy.[3] PTH levels are also characteristically high in secondary hyperparathyroidism - usually associated with renal failure - as a result of constant stimulation of the parathroid gland by low calcium levels. Hypocalcemia accompanied by a low PTH level, on the other hand, is to be expected in hypoparathyroidism, either postsurgical or idiopathic.[1,2,3,4]

PTH Panel: intact PTH, serum total calcium.
The PTH panel is useful for the diagnosis of primary hyperparathyroidism, secondary hyperparathyroidism, and differential diagnosis of hypercalcemia. A nomogram of PTH vs. Ca will accompany the results according to the following tentatively defined ranges.

Differential Diagnosis	**intact PTH (pg/mL)**	**Ca (mg/dL)**
Normal	12-65	8.5-10.1
Primary hyper-parathyroidism	> 65	> 10.2
Secondary hyper-parathyroidism	> 65	< 10.2
Hypo-parathyroidism	< 12	< 9
Non parathyroid hypercalcemia	< 65	> 10.1

PTH group: intact PTH, serum total calcium, creatinine and phosphorous.
The PTH group can be useful in hyperparathyroidism secondary to renal failure.

Note:

The iPTH assay is intended strictly as an aid in the differential diagnosis of hypercalcemia and hypocalcemia, not for the diagnosis or management of malignancy. It is always important to interpret PTH results in the light of total or ionized calcium levels. The finding of a persistently high-normal calcium accompanied by a high-normal PTH (alternatively a low-normal calcium accompanied by a low-normal PTH) warrants further investigation; for the PTH, though itself within normal limits, may still be inappropriately high (or inappropriately low) relative to the circulating calcium level. It should also be remembered that hypercalcemia may be secondary to discovered vitamin D metabolism.

References:

1. Armitage EK. Parathyrin (parathyroid hormone): metabolism and methods for assay. Clin Chem 1986;32:418-24.
2. Blind E, Schmidt-Gayk H, Scharia S, Flentje D, Fischer S, Goehring U, Hitzler W. Two site assay of intact parathyroid hormone in the investigation of primary hyperparathyroidism and other disorders of calcium metabolism compared with a midregion assay. J Clin Endocrinol Metab 1988;67:353-60.
3. Kao PC, Grant CS, Klee GG, Khosla S. Clinical performance of parathyroid hormone immunometric assays. Mayo Clin Proc 1992;67:637-45.
4. Hawker CD, Di Bella FP. Radioimmunoassays for intact and carboxylterminal parathyroid hormone: clinical interpretation and diagnostic significance. Ann Clin Lab Sci 1980;10:76-87.

HCV Viral Load by bDNA

Quantification of HCV RNA before and during treatment of combination interferon and ribavirin can provide important information on the likelihood of response to treatment. Early viral response (EVR), defined as a minimum 2 log decrease in viral load during the first 12 weeks of treatment, is predictive of sustained virological response and should be a routine part of monitoring. Patients who fail to achieve an EVR at week 12 of treatment have only a small chance of achieving a sustained virological response even if therapy is continued for a full year. Treatment needs not be extended beyond 12 weeks in these patients [1]. Determination of HCV viral levels before treatment, at 12 weeks, and 24 weeks of treatment is recommended.[2-3]

This assay is limited to the quantitation of HCV RNA in human plasma or serum to monitor the change of HCV viral load. It is not for diagnosis of HCV infection. A HCV RNA level less than 3200 copies/mL (615 IU/mL) does nor exclude viremia and may reflect only a transient decline in viral level below the detection limit of the assay. A follow up qualitative HCV RNA by TMA (sensitivity = 5-10 IU/mL) or by PCR (sensitivity = 50 IU/mL) should be performed to confirm the absence of active HCV replication.

References:

1. NIH Consensus Development Program Consensus Statement, Management of Hepatitis C: 2002.
2. Dufour DR, Lott JA, Nolte FS, Gretch DR, Koff RS and Seeff LB, "Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests", Clinical Chemistry, 2000; 46:2027-2049.
3. Clinical Implications: Hepatitis in the New Millennium - HCV Molecular Tools, American College of Gastroenterology, 2001