GENOVA DIAGNOSTICS

63 Zillicoa Street
Asheville, NC 28801

CV Health plus genomics

Patient: **SAMPLE PATIENT**
DOB:
Sex:
MRN:

3701 CV Health Plus Genomics- Plasma, Serum & Buccal Swab

Methodology: Chemiluminescent, Enzymatic, Immunoturbidimetric, NMR and PCR

Lipid Markers

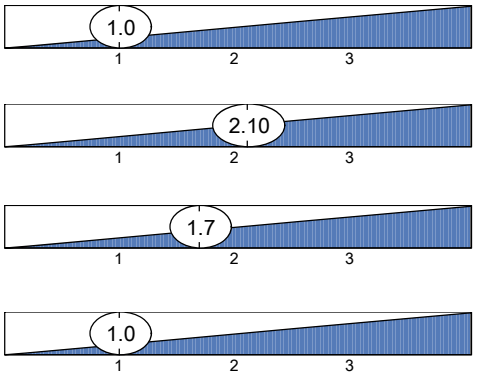
Cholesterol	Result	Reference Range
LDL- Cholesterol	90	< 100 mg/dL
HDL- Cholesterol	48	> 39 mg/dL
Triglycerides	147	< 150 mg/dL
Total Cholesterol	158	< 200 mg/dL

Particle Concentration & Size by NMR	Result		Reference Range
LDL-Particle # (LDL-P)	1,050	H	< 1,000 nmol/L
HDL-Particle # (HDL-P)	2.5	L	> 34.9 µmol/L *
LDL-Size	Large (Pattern A):		Small (Pattern B):
	23.0-20.6 *		20.5-19.0 *
	20.0		
Lp(a)	11		< 30 mg/dL

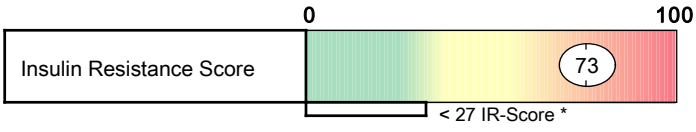
Independent Risk Factors

	Result		Reference Range
hs-CRP	0.89		< 1.00 mg/L
Lp-PLA 2 (PLAC)	245	H	< 225 nmol/min/mL
Fibrinogen	343		198-437 mg/dL
Homocysteine	8.8		3.7 - 10.4 µmol/L

Relative Risk for Cardiovascular Disease



Insulin Resistance Score by Lipid Fractionation



The Insulin Resistance Score combines Small LDL-Particle #, LDL Size, Large VLDL-Particle #, VLDL Size, Large HDL-Particle # and HDL Size to assess insulin resistance and diabetes risk.

HDL L	LDL S	VLDL L	HDL Size	LDL Size	VLDL Size
2.5	255	4.5	8.4	20.0	47.6
>7.3 µmol/L *	<117 nmol/L *	<0.9 nmol/L *	>9.6 nm *	>21.2 nm *	<42.4 nm *

Optimal | Borderline | Abnormal

Percentiles Apply to Biomarkers indicated with * and are performed using NMR technology.

Optimal: Either 0-25th or 75-100th percentile based on reference population.

Borderline: 25-75th Percentile

Abnormal: Inverse of Optimal (0-25th or 75-100th percentile distribution)

Apo E

Apolipoprotein E : CHOLESTEROL REGULATION

Location:
Chromosome 19
APOE
APO E2: cys / cys
APO E3: cys / arg
APO E4: arg / arg
Your Genotype:

3 4

The two SNPs lead to 3 possible variants for each chromosome, known as ApoE2, E3, & E4.

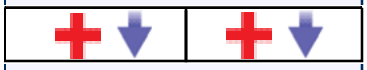
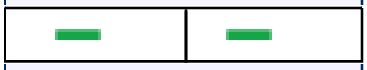
Apolipoprotein E (Apo E) plays a key role in lipid metabolism by helping to remove dietary cholesterol (chylomicrons and VLDL) from the bloodstream.

Health Implications

- The E3/E4 genotype is the second most prevalent after E3/E3, accounting for >25% in most populations.
- ApoE4 confers a tendency toward higher total- and LDL cholesterol, lower HDL-C.
- Increased risk of stroke (esp. among Asians), hypertension, and MI; also increased risk of cognitive impairment after stroke; generally lower CRP levels with E4 allele despite higher CV risk.
- ApoE4 allele may be an independent predictor of CAD and type 2 diabetes, especially in obese individuals and smokers.
- Increased risk of low BMD, oxidative stress, also easier toxicity by heavy metals such as lead and mercury
- ApoE4 may increase risk and disease severity of multiple sclerosis

Clinical Management Considerations

- Stress management: ApoE4 is associated with poor response to life stressors; prolonged stress contributes to memory decline.
- Restriction of saturated fat and cholesterol lowers total- and LDL cholesterol and CAD risk the most effectively in E4 individuals, also reduces risk of MI.
- Avoid smoking and minimize high-glycemic index foods, both of which augment E4-associated risk of CHD.
- Alcohol may raise LDL-C in men (neutral effect in women), increase IL-6 levels, and fail to raise HDL-C.
- Reduce excess weight, which synergizes with effects of E4 on insulin and lipids.
- Fish oils may lower triglycerides but increase LDL-C in E4 carriers; mixed studies.
- Antioxidants may help to counteract low antioxidant tissue levels; anti-inflammatory agents help preserve cognitive function.
- Lipid response to statins, and triglyceride response to fibrates, are usually the most positive in E2 > E3 > E4; studies are mixed.
- Estrogen therapy is particularly efficacious for both cholesterol and bone in postmenopausal E4 carriers.

MTHFR	5,10-methyltetrahydrofolate reductase : METHYLATION
Location: Chromosome 1 **C677T** **Your Genotype:**  **A1298C** **Your Genotype:** 	5,10-methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism, facilitating the formation of methyltetrahydrofolate, a required cofactor in the remethylation of homocysteine (Hcy) to methionine. **Health Implications** · Homozygosity for 677 (+/+) results in 60-70% reduction in MTHFR enzyme activity, which can limit methylation reactions in the body · Increased risk of high homocysteine, esp. when low levels of B vitamins, mainly folate; several studies also indicate a tendency for lower folate levels · Most studies suggest increased risk of venous thrombosis, heart disease, hypertension, stroke and diabetic nephropathy; population differences may reflect the influence of B vitamin fortification, which lowers Hcy · Several studies show moderately increased risks of depression and schizophrenia · Most studies suggest increased risk of birth defects in the offspring, e.g., neural tube or congenital heart defects, cleft lip and/or palate, and Down syndrome; possible increased risk of recurrent pregnancy loss and male infertility in Asians · Possible slight increased risk of fracture and/or low bone density; in some studies these associations depend on B vitamin status, while others show no associations · Increased risk of gastric and esophageal cancer, which may be reversed with adequate folate intake; some studies show higher risk of breast, lung, and cervical cancer in Asians · Decreased risk of colorectal cancer, but only when high folate status; decreased risk of acute lymphoblastic leukemia in children and Caucasians; and decreased risk of cervical cancer in Caucasians **Clinical Management Considerations** · Ensure adequate intake of dark-green leafy vegetables and other B vitamin-rich foods · Consider supplementation with folic acid (or 5-methyltetrahydrofolate, which bypasses the MTHFR step), B2, B6 (pyridoxal 5-phosphate), B12 (or methylcobalamin), and betaine (trimethylglycine) · Most studies suggest easier toxicity from chemotherapy

FACTOR II

Location:
Chromosome 11
G20210A
Your Genotype:

Factor II (Prothrombin) : COAGULATION

Factor II is also known as prothrombin, which is converted to its active form, thrombin, and forms the essential part of a blood clot.

Health Implications

· Elevated levels of prothrombin, with 3.8-fold increased risk of venous thrombosis; risk increases 20-fold if coexisting Factor V Leiden SNP

· Increased chance of atherosclerosis, atrial fibrillation, and heart attack

· Slightly increased risk of pre-eclampsia during pregnancy

Clinical Management Considerations

· Avoid oral contraceptives, HRT, and smoking

· Platelet activation inhibitors include: fish oils, garlic, onions, ginger, ginkgo biloba, thyme, rosemary, genistein, and aspirin

· Glycyrrhizin (licorice) inhibits conversion of prothrombin to thrombin

FACTOR V

Location:
Chromosome 1
R506Q
Your Genotype:

Factor V (Leiden) : COAGULATION

Factor V combines with Factor X to convert prothrombin to thrombin, the essential part of a blood clot. Factor Va is held in check by Protein C.

Health Implications

· Elevated levels of thrombin; 7-fold increased risk of clot formation

· Increased chance of heart attack and atherosclerosis

· Increased risk of miscarriage, pre-eclampsia, and placental abruption

Clinical Management Considerations

· Avoid oral contraceptives; risk of DVT increases 35-fold

· Avoid oral HRT, smoking, high homocysteine

· Platelet activation inhibitors include: fish oils, garlic, onions, ginger, ginkgo biloba, thyme, rosemary, genistein, and aspirin

· Glycyrrhizin (licorice) inhibits conversion of prothrombin to thrombin

· Exercise caution with hypertension

Key

- - Neither chromosome carries the genetic variation.
+ - One chromosome (of two) carries the genetic variation.
+ + Both chromosomes carry the genetic variation.

(You inherit one chromosome from each parent)

+ ▲ Gene activity increased
+ ▼ Gene activity decreased

This test has been developed and its performance characteristics determined by Genova Diagnostics, Inc. It has not been cleared or approved by the U.S. Food and Drug Administration.

Commentary is provided to the practitioner for educational purposes, and should not be interpreted as diagnostic or treatment recommendations. Diagnosis and treatment decisions are the responsibility of the practitioner.

The accuracy of genetic testing is not 100%. Results of genetic tests should be taken in the context of clinical representation and familial risk. The prevalence and significance of some allelic variations may be population specific.

Any positive findings in your patient's test indicate genetic predisposition that could affect physiologic function and risk of disease. We do not measure every possible genetic variation. Your patient may have additional risk that is not measured by this test. Negative findings do not imply that your patient is risk-free.

DNA sequencing is used to detect polymorphisms in the patient's DNA sample. The sensitivity and specificity of this assay is <100%.

The LP(a), Lp-PLA$_2$ (PLAC), hs-CRP, Homocysteine and Fibrinogen analytes have been cleared by the U.S. Food and Drug Administration, and are performed by Genova Diagnostics, Inc. All other assays are performed by LabCorp, 1447 York Court, Burlington, NC 27215, CLIA#34D0655059.

The reference range for homocysteine is based on the sex-specific 5th to 95th percentile values for men and women (20 to 39 years of age) in the NHANES nutritionally replete cohort. Annals of Internal Medicince 1999; 131 (331-338).

The methodology for Lp-PLA$_2$ (PLAC) has been changed to measure activity. Please note the reference range and relative risk for cardiovascular disease have been updated.

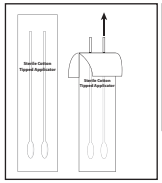


figure 1


figure 2

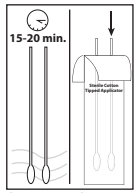
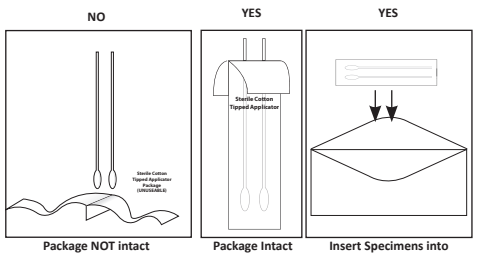


figure 3A figure 3B

(REPEAT FIGURES 1 - 3)



Package NOT intact SPECIMEN UNUSABLE!! | Package Intact Specimen Usable | Insert Specimens into Letter Envelope

SPECIMEN PREPARATION

1. **Plan** to ship the specimen Monday – Thursday overnight delivery.
2. **Call** 1.800.GoFedEx (1.800.463.3339) to schedule shipping. When the automated system asks "How may I help you?" **say** "Return a Package". **Tell** the FedEx representative "I am using a billable stamp"and they will walk you through the process and make it easy.
3. **Place** the envelope containing the two collected specimen swabs into the Biohazard bag. Make sure the 1 serum transfer tube, 1 plasma transfer tube, and the black-top tube **are tightly closed** and **identified** with completed labels. **Seal** the tubes in the bubble wrap bag and **put** it into the Biohazard bag, and seal it securely. *If Vitamin D add-on ordered, there will be 2 serum transfer tubes returned to the laboratory.*
4. **Print** name and collection date on specimen collection label. **Place** the specimen collection label on the biohazard bag.
5. **Lay** the Biohazard bag with specimen on top of the freezer brick in the foam box. **Secure** the foam box lid with the rubber band.
6. **Slide** the foam box back inside the kit box, and **place** the completed and signed requisition on top before closing. **Do not staple** or **tape** the box.
7. **Print** your name and address in the section marked "From" on the prepaid shipping envelope label. **DO NOT mark or write** in any other sections.
8. **Put** the kit box into the envelope and **seal** the envelope.
9. **Keep** your shipment and tracking numbers for future reference and tracking purposes.

GENOVA DIAGNOSTICS

ASHEVILLE • ATLANTA • LONDON

63 Zillicoa Street • Asheville NC 28801 • 800.522.4762 • www.gdx.net

 GDX IS-K94,n,pi,b-525-u,062510 rev 0515

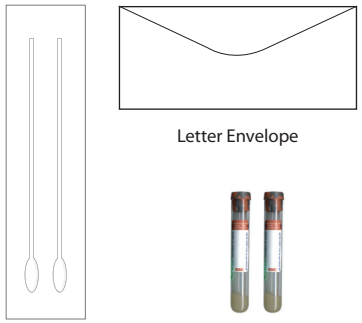
CV HEALTH & CV HEALTH PLUS GENOMICS SPECIMEN COLLECTION INSTRUCTIONS

This specimen collection kit can be used for the following tests:

CV Health Profile™

CV Health Plus Genomics Profile™*

* Not Available in New York


Cotton Swabs and Package

Letter Envelope

2 SST tubes


1 black-top tube


3 Transfer tubes (2 serum & 1 plasma)


2 pipettes


6ml lavender-top tubes

SPECIMEN

Buccal swab - saliva, Blood

COLLECTION MATERIALS

- Cotton Swabs
- Returnable Cotton Swabs Package
- Letter Envelope
- 6 ml EDTA lavender-top tube
- 2 SST tubes
- 3 Transfer tubes (2 serum & 1 plasma)
- 1 Black-top tube
- 2 Pipettes

SHIPPING MATERIALS*

- 1 Foam Insulator Box
- 1 Freezer Brick
- Specimen collection kit package
- Test Requisition Form
- 2 Biohazard bags with side pocket
- 1 Absorbant Pad
- FedEx® Clinical Lab Pak and Billable Stamp
- 3 Specimen Collection Labels

International shipping may vary, please see shipping instructions for more details.

IMPORTANT:

All patient specimens require two unique identifiers (***patient's name and date of birth***), as well as ***date of collection***. **Patient's first and last name, date of birth, gender,** and **date of collection** must be recorded on the **Test Requisition Form** as well as all tube(s) and/or cup(s), using a permanent marker, or the test may not be processed.

GENOVA DIAGNOSTICS

Please read all instructions carefully before beginning.

PATIENT PREPARATION

- Certain medications and supplements may influence this test, including aspirin and cholesterol-lowering drugs. Results may help demonstrate the efficacy of medications or supplements, or a clinician may elect to have the patient temporarily discontinue non-essential ones.
- Specimens from patients who are on drug therapy involving S-adenosyl-methionine may show elevated levels of homocysteine.
- Hemolyzed and lipemic specimens interfere with the test and cannot be accepted for analysis.
- Results on specimens obtained from patients taking methotrexate, carbamazepine, phenytoin, nitrous oxide, anti-convulsants, or 6-azauridine triacetates should be interpreted with caution as these substances interfere with homocysteine determination.
- **On the day before the collection**: Patients must fast overnight (at least 12 hours) prior to the blood draw. Patients should also be counseled to avoid exercise for at least 12 hours prior to the test, and to avoid alcohol consumption for at least 24 hours prior to the test.

SCHEDULE & PREPARE FOR THE BLOOD DRAW

- **Schedule** the patient accordingly
- **Freeze** the enclosed freezer brick a minimum of 8 hours before shipping.
- Samples **MUST be received** within 24 hours of collection. The test cannot be processed otherwise.
- **Contact** FedEx and schedule to ship the specimen overnight delivery Monday - Thursday. All serum and plasma transfer tubes MUST be stored frozen a minimum of 2 hours before shipping.
- **Complete** the Requisition Form with all patient and billing information. Be sure it is signed by the Patient/Responsible Party and the healthcare provider.

BLOOD DRAW & SPECIMEN PREPARATION

1. **Write** patient's **first and last name, date of birth**, **gender** and **date of collection** on the Test Requisition Form (located in the pouch on top of the Specimen Collection Kit Envelope), and the SST, lavender-top EDTA, transfer tubes, AND the collection labels. **Affix** collection labels to the black-top tube.
2. **Draw** blood to fill one SST tube (Serum), 6ml lavender-top EDTA tube, and black-top tube. The black-top tube **must be completely filled**. *If Vitamin D add-on is ordered, **fill** both SST tubes.* SST tube(s) and 6ml EDTA specimen **should be stored on ice** between the time of sampling and centrifugation.
3. **6ml lavender-top EDTA tube**: Within 15 minutes of blood draw, gently **mix** blood sample thoroughly. **Centrifuge** 6ml lavender-top EDTA 15 minutes at 3000 rpm.
4. **Use** a pipette to transfer the plasma from the 6ml lavender top tube into the transfer tube labeled "EDTA-Plasma". **Freeze** the plasma transfer tube and **discard** the 6ml lavender-top EDTA tube.
5. **SST tube: Allow** blood to clot by placing SST tube in a rack for 15 minutes, then centrifuge the tube for 15 minutes at 3000 RPM. *If Vitamin D add-on is ordered, **follow** this step for both SST tubes.*
6. **Transfer** serum from the SST tube into the transfer tube labeled "SST-Serum" using a fresh pipette. **Screw** the top on the transfer tube tightly to avoid leakage. **Freeze** the serum transfer tube and discard the SST collection tube. *If Vitamin D add-on is ordered, **freeze** the second transfer tube.*
7. **Black-top tube:** Within 30 minutes of blood draw, gently **invert** the tube to mix contents and allow sample to clot for 30 minutes before centrifugation. **Centrifuge** the tube for 15 minutes at 3000 RPM. **Leave** specimen intact and refrigerate black-top tube.
8. **If ordering Genomics** continue through #13, **Peel** open the package labeled, "Sterile Cotton Tipped Applicator." *Only peel back the package far enough to remove the cotton swab applicator*. Keep the packet in-tact. (See Figure1). **Open** your mouth widely and insert applicator. **Wipe** the inside of your cheek using a back and forth and up and down motion. **Rotate** the applicator several times to ensure the swab collects a sufficient amount of cheek cells. *Note: If there is not enough DNA collected on the applicator, a recollection will be required.*
9. **Remove** one applicator taking care to avoid contact with the cotton tip.
10. **Open** your mouth widely and insert applicator. For at least 30 seconds, **aggressively scrape** the inside of your cheek using a back and forth, and up and down motion. Be sure to **rotate** the applicator several times to ensure the swab collects a sufficient amount of cheek cells. In addition, **swab** between the cheek and gums. (See Figure 2)
    Note: If there is not enough DNA collected on the applicator, a recollection will be required.
11. **Remove** the applicator from your mouth and allow cotton tips to air dry for 15-20 minutes (See Figure 3A) before placing it back into the original packaging, cotton swab first. (See Figure 3B)
12. **Repeat** the collection process (steps 1-3) with the second applicator on your opposite cheek.
13. **Place** the package containing the two collected specimen swabs into the letter envelope. Seal the letter envelope.