

Cardio Check

An Advanced Assessment of Cardiovascular and Metabolic Risk

Lahnor Powell, ND, MPH

Atlanta Medical Education Specialist | Department of Medical Affairs | Genova Diagnostics

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Lahnor Powell, ND, MPH

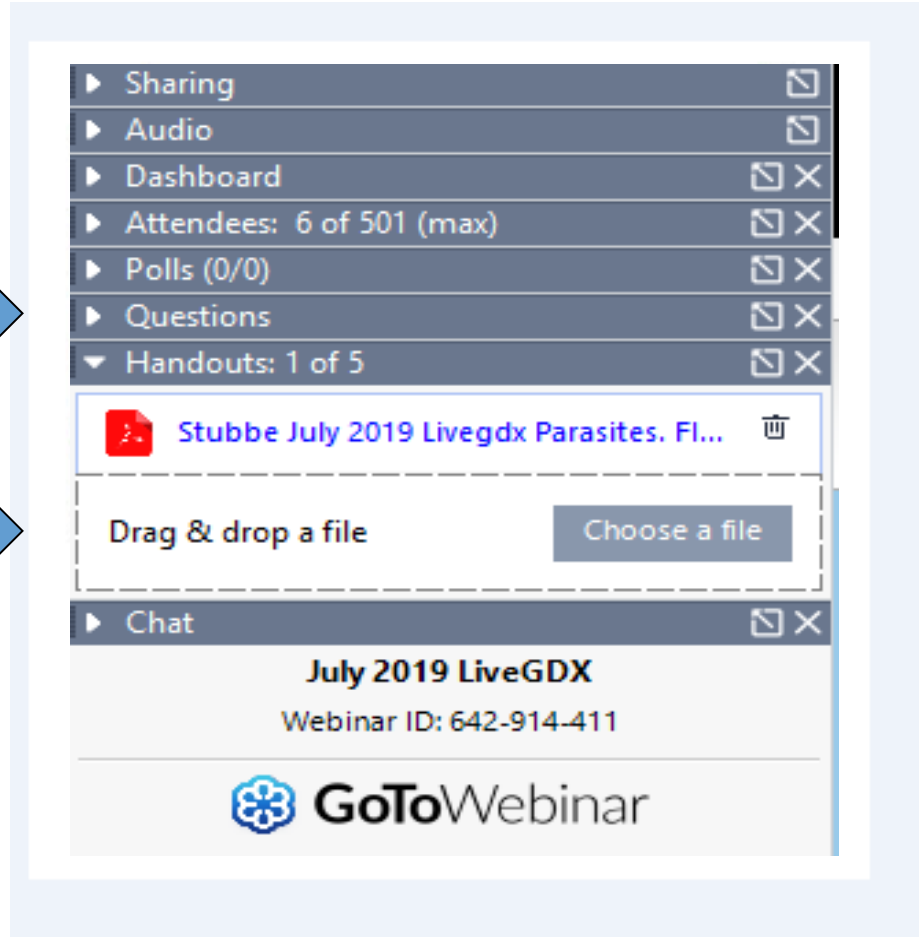
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Technical Issues & Clinical Questions

Please type any technical issue or clinical question into either the “Chat” or “Questions” boxes, making sure to send them to “Organizer” at any time during the webinar.

We will be compiling your clinical questions and answering as many as we can the final 15 minutes of the webinar.



DISCLAIMER: *Please note that any and all emails provided may be used for follow up correspondence and/or for further communication.*

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Need More Resources?

Explore

WWW.GDX.NET

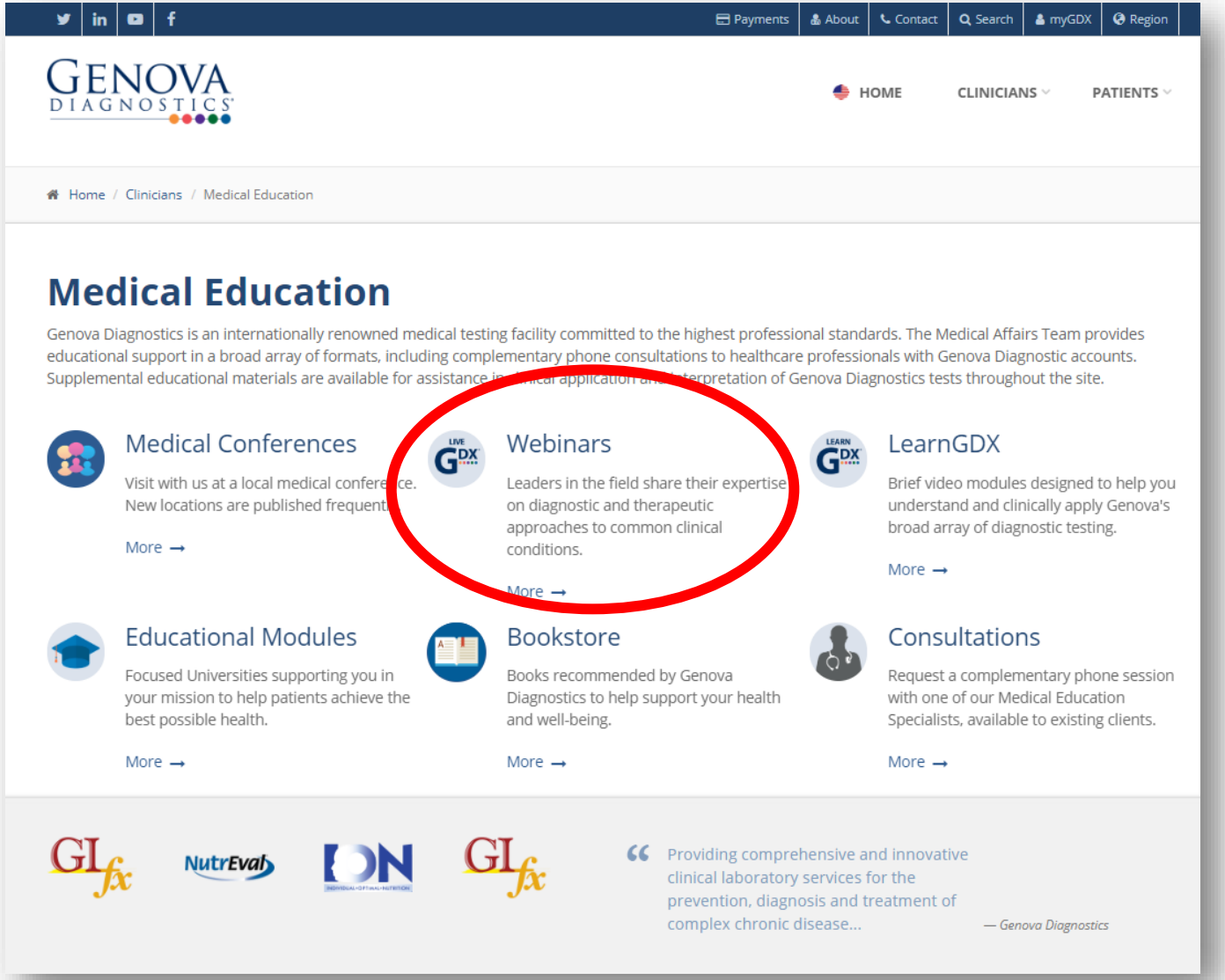
for more information and educational resources, including…

LEARN **GDX** – Brief video modules

LIVE **GDX** – Previous webinar recordings

GI University – Focused learning modules

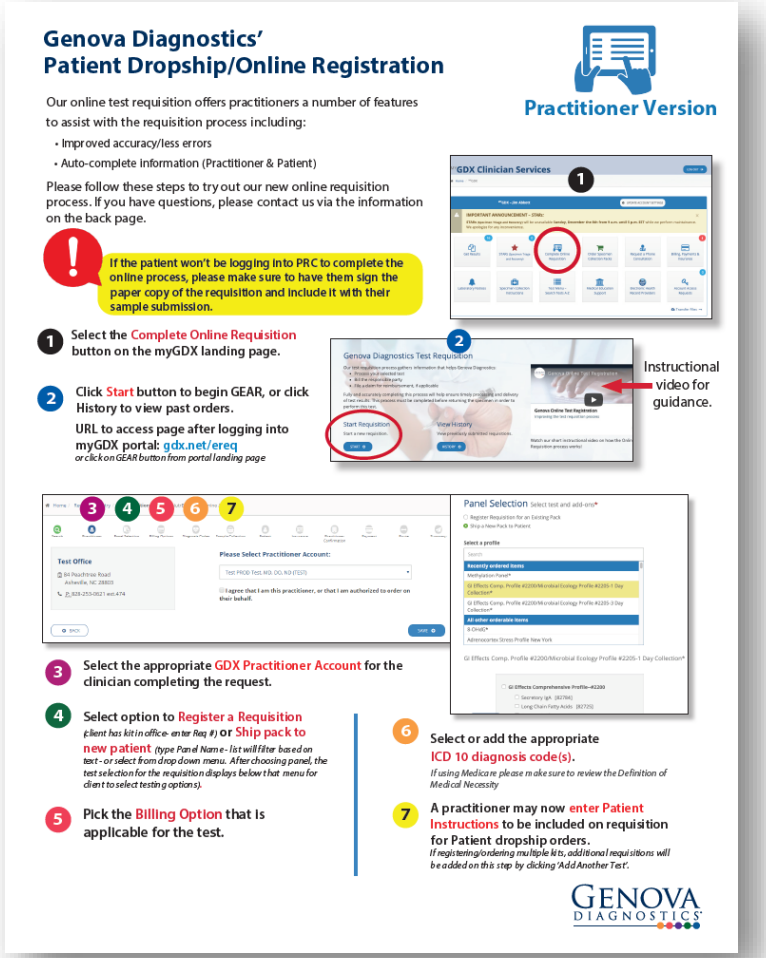
MY **GDX** – Order materials and get results



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Patient Dropship/Online Registration

https://youtu.be/YHd0lD9GVG4



Genova Diagnostics' Patient Dropship/Online Registration

Practitioner Version

Our online test requisition offers practitioners a number of features to assist with the requisition process including:

- Improved accuracy/less errors
- Auto-complete information (Practitioner & Patient)

Please follow these steps to try out our new online requisition process. If you have questions, please contact us via the information on the back page.

If the patient won't be logging into PRC to complete the online process, please make sure to have them sign the paper copy of the requisition and include it with their sample submission.

1 Select the Complete Online Requisition button on the myGDX landing page.

2 Click Start button to begin GEAR, or click History to view past orders.

URL to access page after logging into myGDX portal: gdx.net/ereq
or click on GEAR button from portal landing page

Instructional video for guidance.

3 Select the appropriate GDX Practitioner Account for the clinician completing the request.

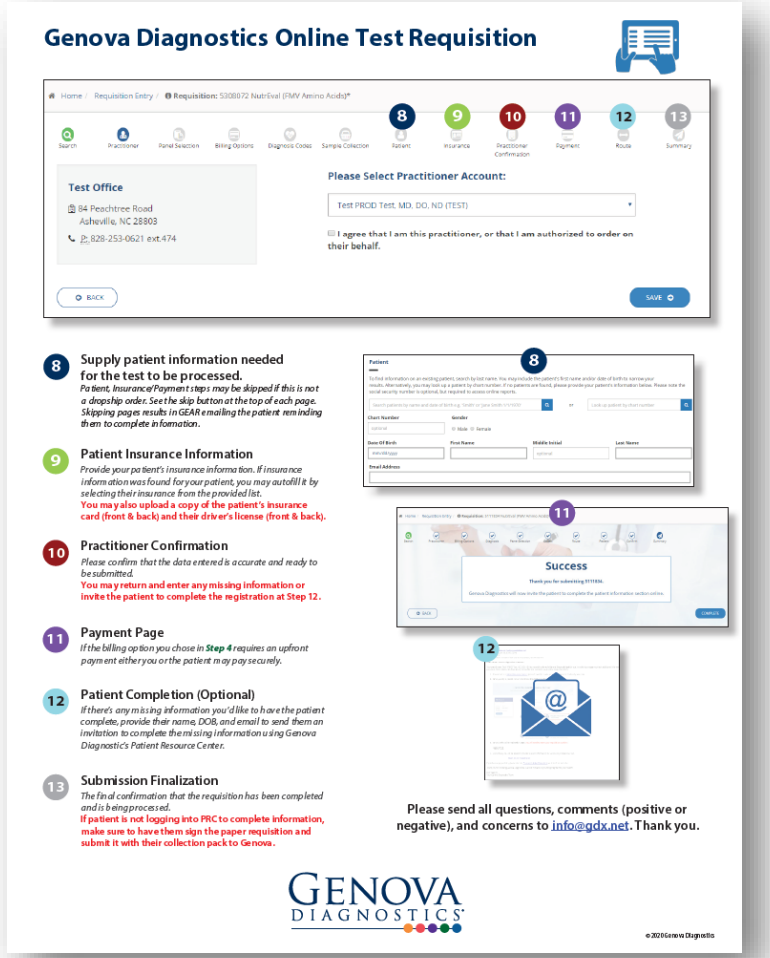
4 Select option to Register a Requisition *(client has kit in office- enter Req #)* or Ship pack to new patient *(type Panel Name - list will filter based on text - or select from drop down menu. After choosing panel, the test selection for the requisition displays below that menu for client to select testing options).*

5 Pick the Billing Option that is applicable for the test.

6 Select or add the appropriate ICD 10 diagnosis code(s).
If using Medicare please make sure to review the Definition of Medical Necessity

7 A practitioner may now enter Patient Instructions to be included on requisition for Patient dropship orders.
If registering/ordering multiple kits, additional requisitions will be added on this step by clicking 'Add Another Test'.

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Genova Diagnostics Online Test Requisition

8 Supply patient information needed for the test to be processed.
Patient, Insurance/Payment steps may be skipped if this is not a dropship order. See the skip button at the top of each page. Skipping pages results in GEAR emailing the patient reminding them to complete information.

9 Patient Insurance Information
Provide your patient's insurance information. If insurance information was found for your patient, you may autofill it by selecting their insurance from the provided list.
You may also upload a copy of the patient's insurance card (front & back) and their driver's license (front & back).

10 Practitioner Confirmation
Please confirm that the data entered is accurate and ready to be submitted.
You may return and enter any missing information or invite the patient to complete the registration at Step 12.

11 Payment Page
*If the billing option you chose in **Step 4** requires an upfront payment either you or the patient may pay securely.*

12 Patient Completion (Optional)
If there's any missing information you'd like to have the patient complete, provide their name, DOB, and email to send them an invitation to complete the missing information using Genova Diagnostics Patient Resource Center.

13 Submission Finalization
The final confirmation that the requisition has been completed and is being processed.
If patient is not logging into PRC to complete information, make sure to have them sign the paper requisition and submit it with their collection pack to Genova.

Please send all questions, comments (positive or negative), and concerns to info@gdx.net. Thank you.

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An Advanced Assessment of Cardiovascular and Metabolic Risk

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Overview of this Presentation

- Review what is known and understood about atherosclerosis
- Review the components of the Cardio Check Profile
- Discuss modifiable CVD risk factors



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Atherosclerosis

- It begins in **childhood** with a “fatty streak” – over the years this progresses, and disease doesn’t usually manifest until later in life
- Plaque is made up of cholesterol, cellular waste products, calcium, and fibrin (a blood clotting molecule)
- Plaque builds up in the arteries which leads to:
  - Thickening of the blood vessel wall and narrowing of the channel
  - Reducing blood flow
- Plaque that completely narrows the channel, or breaks off and lodges somewhere downstream can lead to cell and tissue death

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Minelli S, et al. *J Multidiscip Healthc.* 2020;16:621-633.

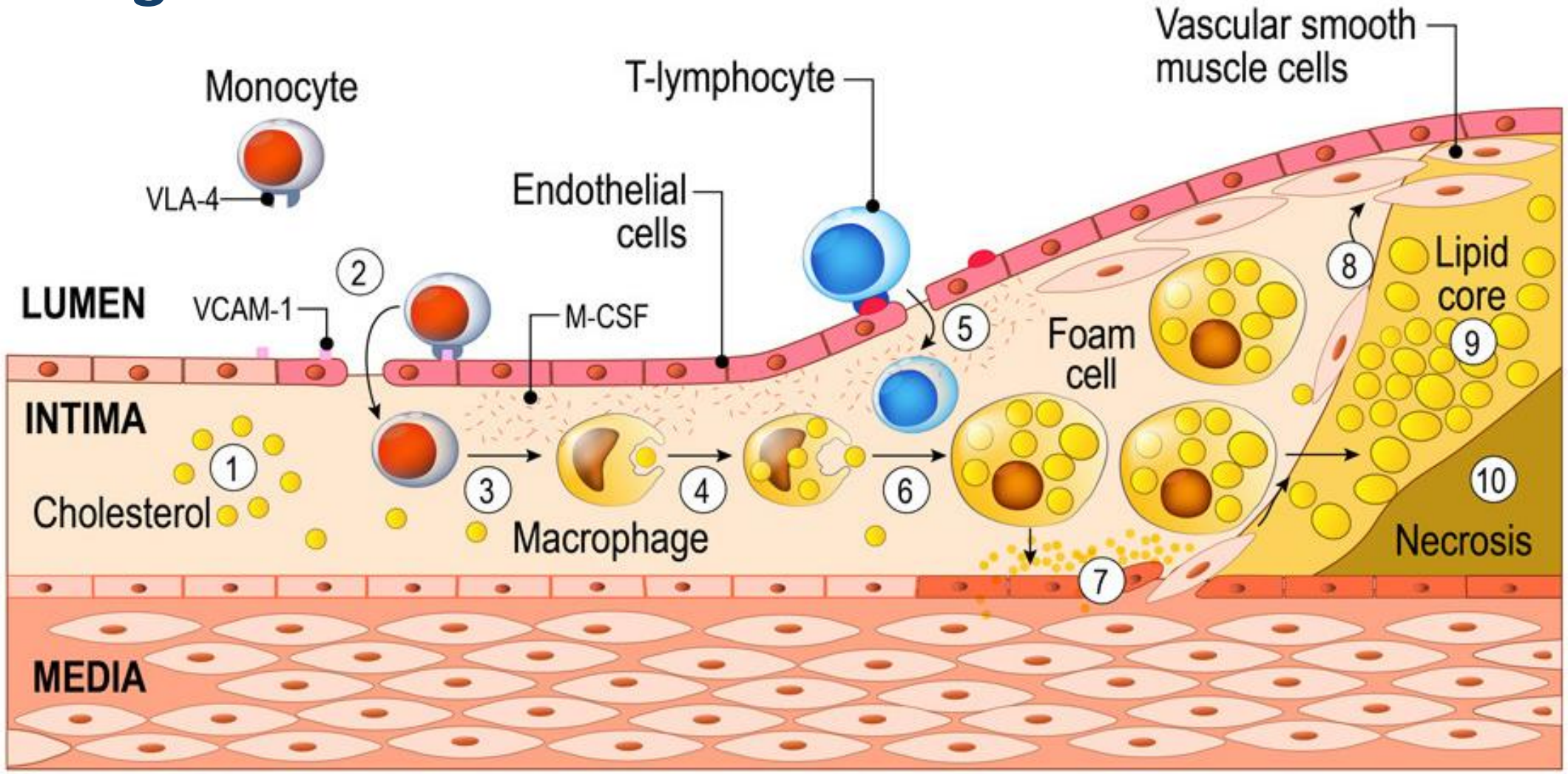
What We Know about Atherosclerosis

- Initiating event = **endothelial dysfunction** or the response-to-injury theory
  - Insult to endothelium by a variety of sources
    - Oxidative Stress
    - Inflammation
    - Hypertension
    - Insulin resistance
    - Sedentarism
- Endothelial dysfunction leads to vascular permeability
- Infiltration of cholesterol and immune cells (neutrophils and macrophages)
- Inflammation and plaque formation

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Minelli S, et al. *J Multidiscip Healthc.* 2020;16:621-633.

Pathogenesis of Atherosclerosis



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Minelli S, et al. *J Multidiscip Healthc.* 2020;16:621-633.

Atherosclerosis Consequences

- Precursor to many diseases
  - Heart disease, angina, high blood pressure (hypertension), stroke, heart failure, rheumatic heart disease, cardiomyopathies, peripheral vascular disease, etc.
- Where the plaque builds up/breaks off (embolism), it leads to disease in that region
  - Coronary artery disease, Carotid artery disease, Peripheral artery disease , and Chronic kidney disease

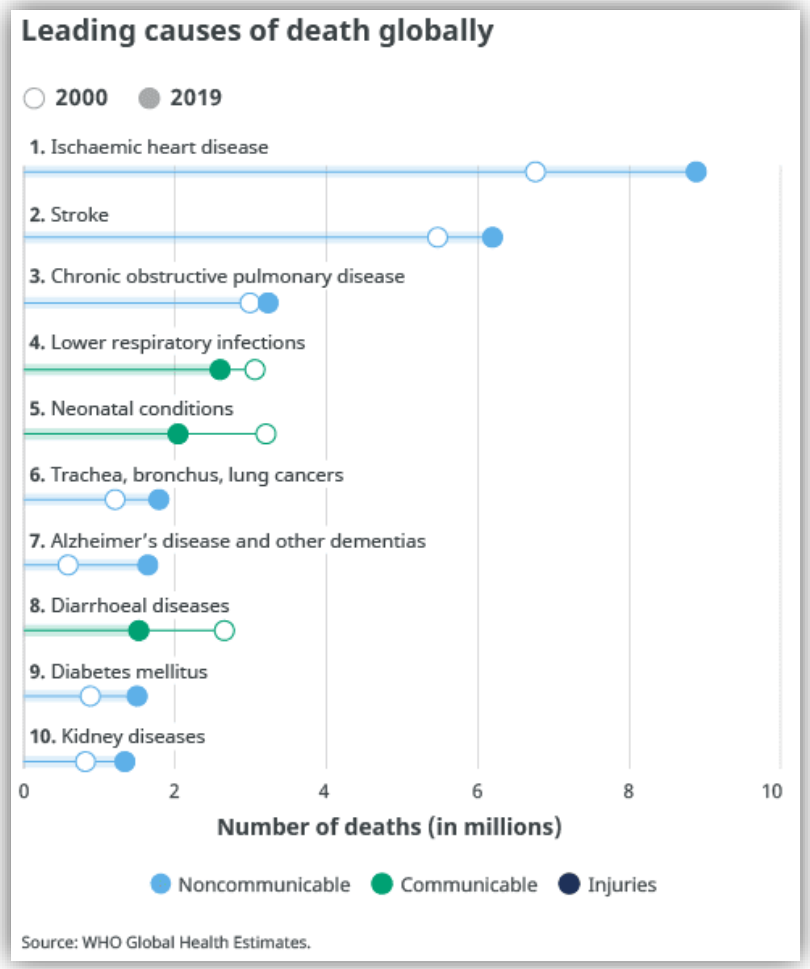


Image: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.

Minelli S, et al. *J Multidiscip Healthc.* 2020;16:621-633.

The NEW ENGLAND JOURNAL of MEDICINE

Review Article

Mechanisms of Disease

FRANKLIN H. EPSTEIN, M.D., *Editor*

ATHEROSCLEROSIS — AN INFLAMMATORY DISEASE

"Thus, although hypercholesterolemia is important in approximately 50 percent of patients with cardiovascular disease, other factors need to be taken into consideration. Atherosclerosis is clearly an inflammatory disease and does not result simply from the accumulation of lipids."

to be the principal cause of death in the United States, Europe, and much of Asia.[4,5] In fact, the lesions of atherosclerosis represent a series of highly specific cellular and molecular responses that can best be described, in aggregate, as an inflammatory disease.[6-10]

The lesions of atherosclerosis occur principally in large and medium-sized elastic and muscular arteries and can lead to ischemia of the heart, brain, or extremities, resulting in infarction. They may be present throughout a person's lifetime. In fact, the earliest type of lesion, the so-called fatty streak, which is common in infants and young children,[11] is a pure inflammatory lesion, consisting only of monocyte-derived macrophages and T lymphocytes.[12] In persons with hypercholesterolemia, the influx of these cells is preceded by the extracellular deposition of amorphous and membranous lipids.[11,13] By asking ques-

FACTORS THAT INDUCE AND PROMOTE INFLAMMATION OR ATHEROGENESIS

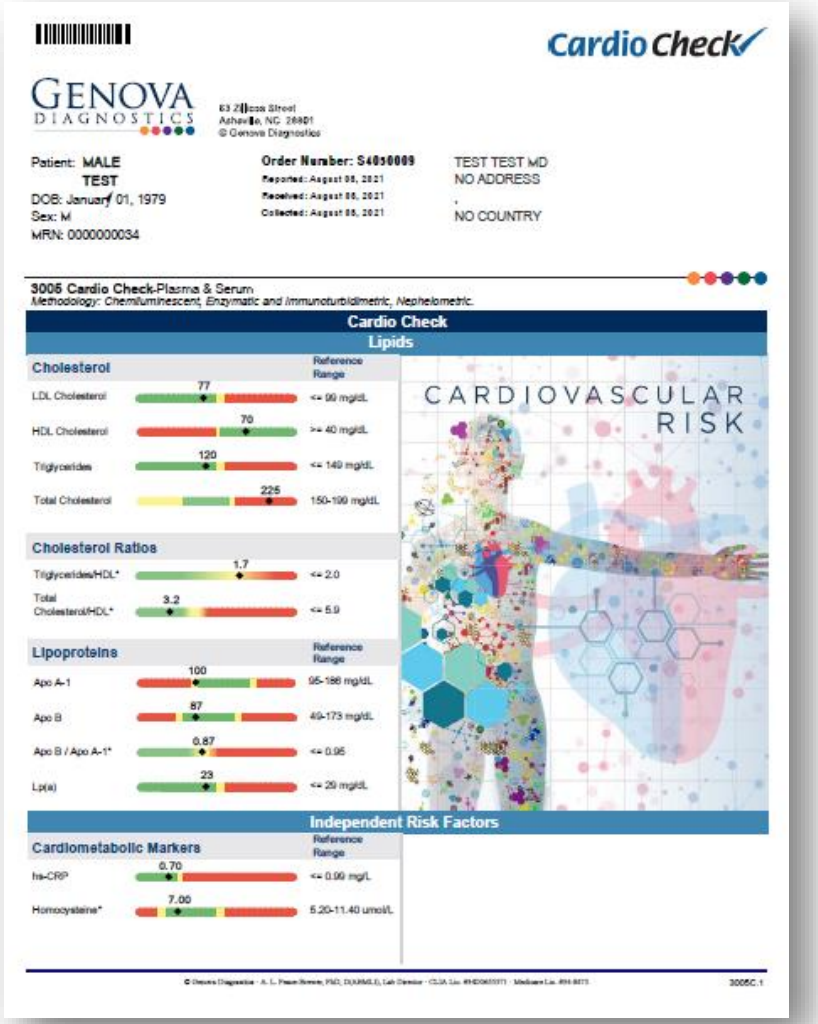
Numerous pathophysiologic observations in humans and animals led to the formulation of the response-to-injury hypothesis of atherosclerosis, which initially proposed that endothelial denudation was the first step in atherosclerosis.[6] The most recent version of this hypothesis emphasizes endothelial dysfunction rather than denudation. Whichever process is at work, each characteristic lesion of atherosclero-

normal homeostatic properties of the endothelium. Thus, the different forms of injury increase the adhesiveness of the endothelium with respect to leukocytes or platelets, as well as its permeability. The injury also induces the endothelium to have procoagulant instead of anticoagulant properties and to form vasoactive molecules, cytokines, and growth factors. If the inflammatory response does not effectively neutralize or remove the offending agents, it can continue indefinitely. In doing so, the inflammatory response stimulates migration and proliferation of smooth-muscle cells that become intermixed with the area of inflammation to form an intermediate lesion. If these responses continue unabated, they can thicken the artery wall, which compensates by gradual dilation, so that up to a point, the lumen remains unaltered,[15] a phenomenon termed "remodeling." As for the inflammatory cells, granulocytes are rarely present dur-

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Cardio Check Profile – A Comprehensive CV Assessment

- The **Cardio Check Profile** is an advanced blood assessment of lipids and cardiometabolic analytes providing insight regarding independent risk
- By combining the best of both conventional and novel biomarkers, it offers a broader look at cardiac health to guide therapeutic strategies.



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Lipids

Cholesterol		Reference Range
LDL Cholesterol	78	<= 99 mg/dL
HDL Cholesterol	70	>= 40 mg/dL
Triglycerides	130	<= 149 mg/dL
Total Cholesterol	170	150-199 mg/dL

Cholesterol Ratios		
Triglycerides/HDL*	1.9	<= 2.0
Total Cholesterol/HDL*	2.43	<= 5.99

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LDL (low density lipoprotein) Cholesterol

- Considered ‘bad cholesterol’ because it can deposit in plaques in arteries leading to atherosclerosis
  - About 60-70% of cholesterol in the body is carried as LDL-C in the blood
  - Primary target of cholesterol-lowering therapy
  - LDL oxidation dramatically increases the proatherogenic effect of LDL
- Elevations associated with atherosclerosis, potentially leading to:
  - Coronary artery disease
  - Stroke
  - Peripheral artery disease

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Brites F, et al. *BBA Clin*. 2017;8:66-77.
Lee Y, Siddiqui WJ. Cholesterol Levels. In: StatPearls: StatPearls Publishing Inc.2021.

HDL (high density lipoprotein) Cholesterol

- Promotes reverse cholesterol transport, carrying LDL cholesterol away from the arteries and back to the liver to be excreted as bile (‘good cholesterol’)
  - Antioxidant, anti-inflammatory properties, and anti-thrombotic properties
- Elevations are associated with:
  - Decreased risk of atherosclerotic plaque formation
- Low levels are associated with:
  - Increased risk of Atherosclerotic Cardiovascular Disease (ASCVD)

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Stadler JT, et al. *Biomedicines*. 2021;9(3).
Sacks FM, et al. *Circulation*. 2017;136(3):e1-e23.
Huff T, et al. Physiology, Cholesterol. In: StatPearls: StatPearls Publishing 2021.

Triglycerides

- **Triglycerides** are the most common type of fat in the body and store excess energy from the diet
  - Triglyceride-rich lipoproteins include chylomicrons and VLDL
- Well established independent marker of CVD, atherosclerotic disease risk, and part of diagnostic criteria for metabolic syndrome (along with HDL)

GENOVA DIAGNOSTICS

. Fishbach F. A Manual of Laboratory and Diagnostic Tests. 7 ed: Lippincott Williams & Wilkins; 2004.
. Lee Y, Siddiqui WJ. Cholesterol Levels. In: StatPearls: StatPearls Publishing Inc.2021.
Laufs U, Parhofer KG, Ginsberg HN, Hegele RA. Clinical review on triglycerides. Eur Heart J. 2020;41(1):99-109c.

Total Cholesterol (TC)

- Includes LDL, VLDL, and HDL cholesterol
- Elevated TC correlates with ASCVD (Atherosclerotic Cardiovascular Disease) and associated with elevated BMI and smoking

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Duncan MS, et al. *JAHA.* 2019;8(11):e011433.
Millán J, et al. *Vasc Health Risk Manag*. 2009;5:757-765.

Cholesterol Ratios

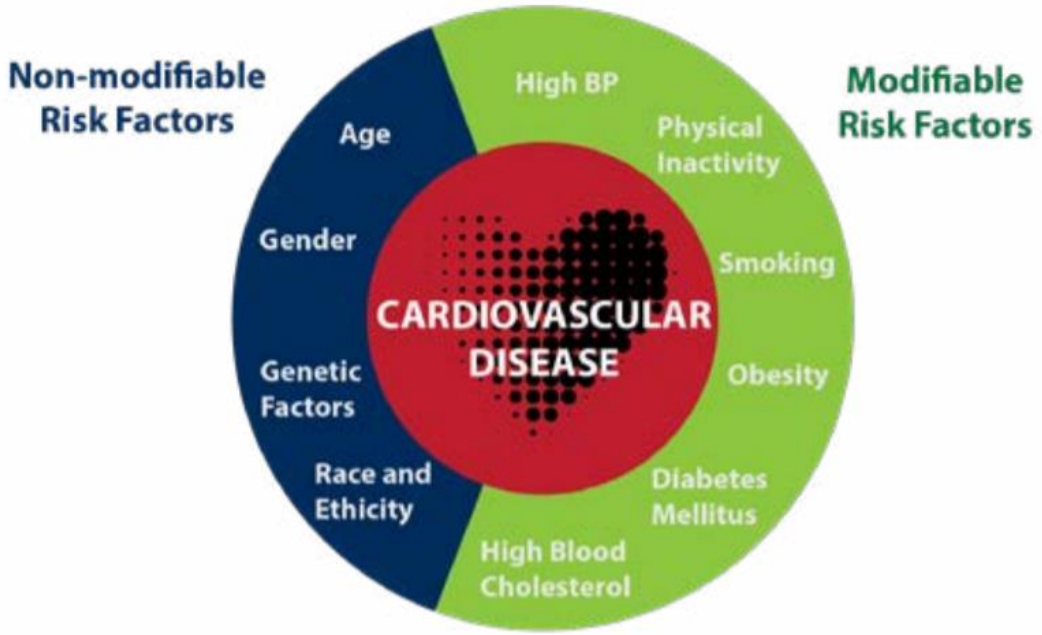
- **Triglycerides : HDL Cholesterol**
  - Shown to predict both metabolic (abdominal obesity, hypertension, and dysglycemia) and cardiovascular risk
  - Associated with insulin resistance
    - Positively correlated with HOMA-IR and serum insulin after OGTT
- **Total Cholesterol : HDL Cholesterol**
  - CHD predictor
    - TC correlates with CVD, whereas HDL has a protective effect. The higher the total-to-HDL ratio, the greater the risk for developing atherosclerosis
    - Ratio reflects the formation of coronary plaques and is a predictor of carotid intima-media thickness
      - A ratio >5 correlates to roughly a 66% increased risk for CHD
      - A ratio >6 correlates to greater than 2x increased risk for CHD

Betzi PT, et al. *Diabetes Metab Syndr.* 2019;13(1):382-388.
Millán J, et al. *Vasc Health Risk Manag*. 2009;5:757-765.
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Nie G, et al. *BMJ Open.* 2021;11(3):e041519.
Murguía-Romero M, et al. *J Lipid Res*. 2013;54(10):2795-2799.
Nur Zati Iwani AK, et al. *Int J Endocrinol.* 2019;2019:8586167.
Fishbach F. A Manual of Laboratory and Diagnostic Tests. 7 ed: Lippincott Williams & Wilkins; 2004.
Arsenault BJ, et al. *JACC*. 2009;55(1):35-41.

Lipids

Lipids are <u>modifiable</u> risk factor for cardiovascular disease

- Diet
  - Reduction in high-glycemic foods
  - Incorporation of whole foods
  - Adequate dietary fiber intake
  - Balance the healthy fats
- Regular physical activity
- Weight loss, if appropriate (BMI)
- Smoking cessation
- HPA axis balance/Stress Management

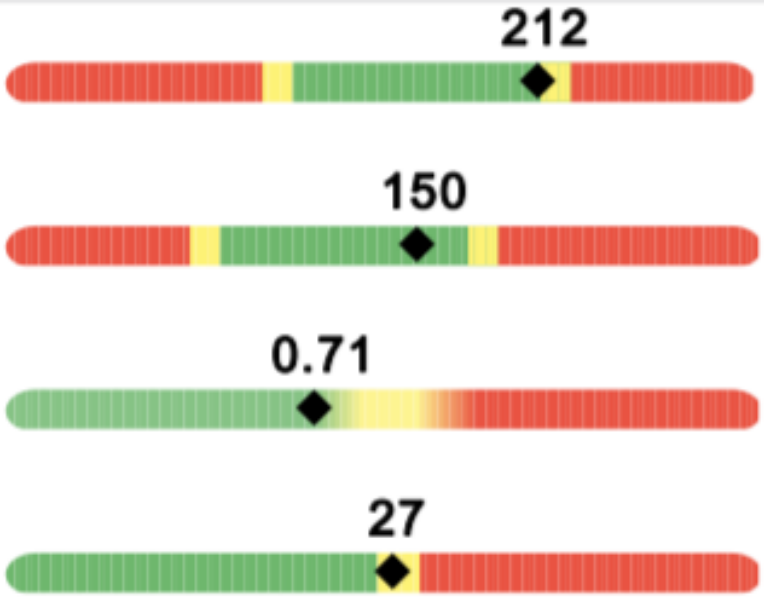


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Refer to slide 35 for citations

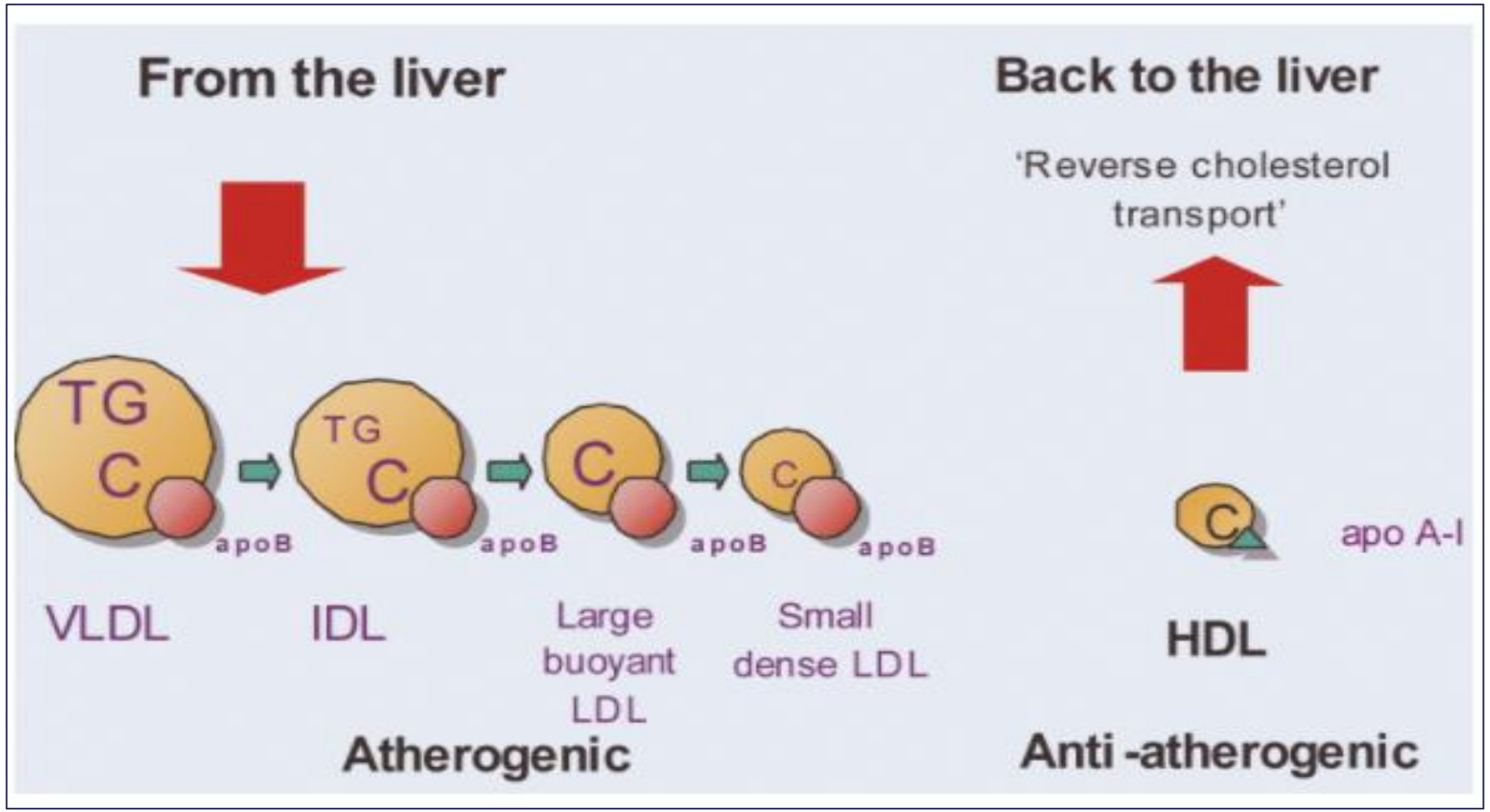
Lipids

Lipoproteins		Reference Range
Apo A-1	212	101-223 mg/dL
Apo B	150	53-182 mg/dL
Apo B / Apo A-1*	0.71	<= 0.95
Lp(a)	27	<= 29 mg/dL



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Lipoproteins: Apo A-1 and Apo B



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Photo: https://www.intechopen.com/chapters/39545

Apolipoprotein A-1 (Apo A-1)

- Main structural component of HDL
  - Supports the bodies clearance of cholesterol owing to protective anti-atherogenic effect
  - Antioxidant and anti-inflammatory effects
  - Stimulates nitric oxide (NO) which is protective for vascular function
- Elevated Apo A-1 associated with decreased risk of atherosclerosis
- Low Apo A-1 increased CVD
  - Factors that lower Apo A-1: diets high in trans fats, PUFA's, smoking, and certain medications

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Feingold KR, et al., eds. Endotext. South Dartmouth (MA): MDText.com, Inc.2000.
Renee Ruhaak L, et al. *Ann Clin Biochem.* 2019;56(3):338- 356.
Fishbach F. A Manual of Laboratory and Diagnostic Tests. 7 ed: Lippincott Williams & Wilkins; 2004.
Sacks FM, et al. *Circulation*. 2017;136(3):e1-e23

Apo B

- Main structural component of atherogenic lipoprotein particles (i.e. LDL, IDL, VLDL, and Lp(a))
  - More than 90% of all Apo B in blood is from LDL
  - Stronger indicator for atherogenicity than LDL-C alone
- Elevations associated with:
  - Health Conditions:
    - Atherosclerosis, CVD, Premature CHD, Diabetes/Insulin resistance, Hypothyroid, Kidney disease, etc…
  - Foods:
    - Trans-fatty acids and saturated fats

Walldius G, et al. *J Int Med.* 2006;259(5):493- 519.

Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143.

Fishbach F. A Manual of Laboratory and Diagnostic Tests. 7 ed: Lippincott Williams & Wilkins; 2004

Feingold KR, et al., eds. Endotext: MDText. com, Inc. 2000.

Chiang AN, et al. *Life Sci.* 1995;56(26):2367-2375.

Haas ME, et al. *Trends Endocrinol Metab TEM.* 2013;24(8):391-397.

Lim HH, et al. *Clin Nutr Res.* 2016;5(3):204-212.

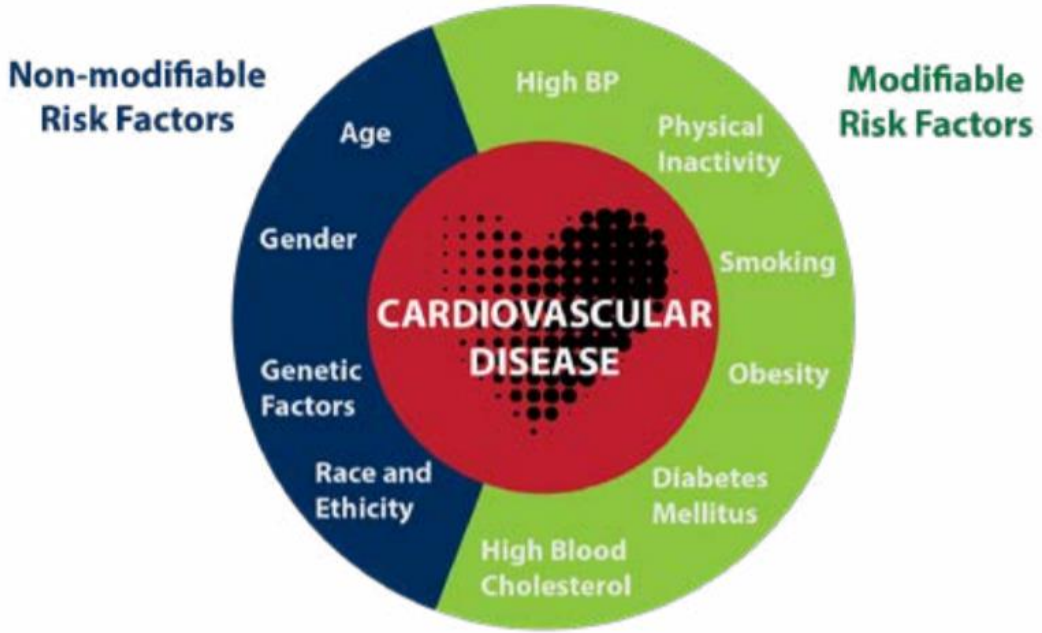
Apo B : Apo A-1 Ratio

- A higher **ApoB/ Apo A-1 ratio** indicates that more atherogenic particles are circulating leading to atherosclerosis and higher risk of CVD events
  - Ratio shown to have a higher predictive ability for metabolic syndrome, CVD, obesity, insulin resistance, diabetes, MI, and early atherosclerosis as compared to standard lipid evaluation

Lu M, et al. *J Biomed Res.* 2011;25(4):266-273.
Nurtazina A, et al. *Diagnostics*. 2020;10(8).
Reynoso-Villalpando GL, et al. *Endocrinol Diab Nutr*. 2019;66(8):502-511.
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Jing F, et al. *Lipids Health Dis*. 2014;13:81.
Kaneva AM, et al. *Dis Mark*. 2015;2015:591454.
Souza PAL, et al. *Nutrients*. 2017;9(10).

Apo A-1 and Apo B

- Apo A-1 and Apo B are **modifiable** risk factor for cardiovascular disease

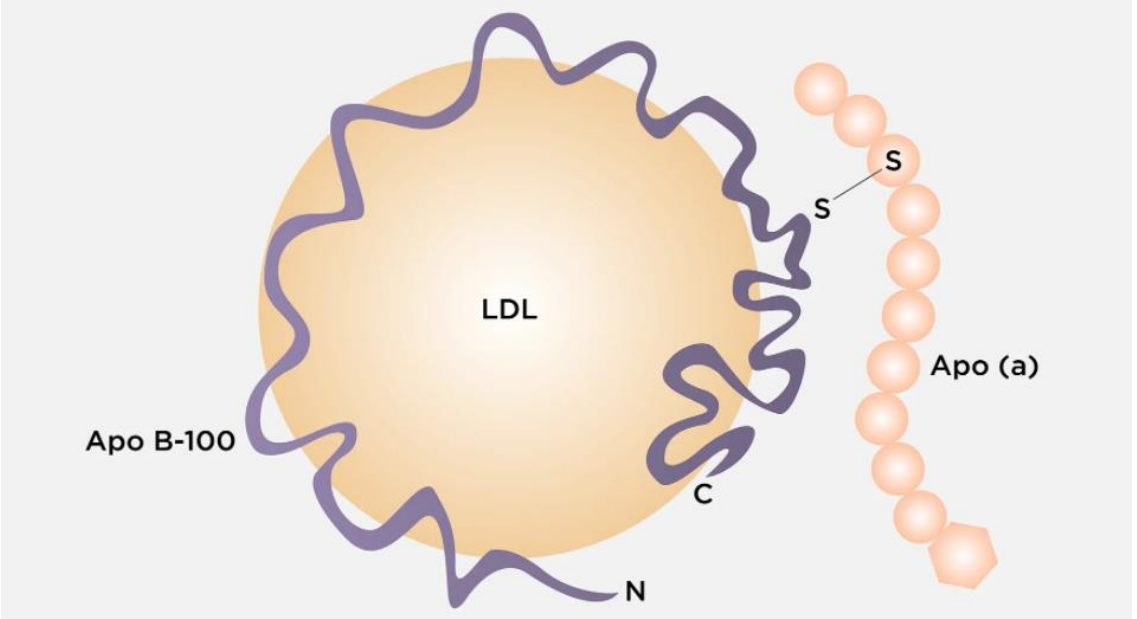


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Ras RT, et al. *Br J Nutr*. 2014;112(2):214-219.
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Lipoprotein(a) or Lp(a)

- Lp(a) is type of lipoprotein
- Lp(a) carries the atherogenic risk by causing damage via inflammation and oxidative stress
  - Inhibits PAI-1
    - Reduced fibrinolysis
  - Carries oxidized phospholipids
    - Attracts inflammation and potentiates atherothrombosis



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Photo: https://thefhfoundation.org/lipoprotein-a-5-things

Momtazi-Borojeni AA, et al. *J Cell Phys.* 2019;234(8):12581-12594.
Tsimikas S.. *JACC.* 2017;69(6):692-711.

Lipoprotein(a) or Lp(a)

- Lp(a) is a **non-modifiable** risk factor for cardiovascular disease
  - Primarily genetically determined by *LPA* gene
  - Can't be modified by diet or exercise
    - Decrease Lp(a): L-carnitine, coenzyme Q10, and red yeast rice
    - Modest reduction: Pectin, Ginkgo biloba, flaxseed, red wine, resveratrol, and curcuminoids

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Momtazi-Borojeni AA, et al. *J Cell Phys.* 2019;234(8):12581-12594.

Independent Risk Factors

Cardiometabolic Markers		Reference Range
hs-CRP	0.70 	<= 0.99 mg/L
Homocysteine*	7.0 	3.7-10.4 µmol/L

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High-sensitivity C-Reactive Protein (hsCRP)

- Acute-phase response protein
  - Produced by liver and extrahepatic tissues
  - Triggered by IL-6, IL-1β, TNF, and other inflammatory stimuli
- High levels strongly correlate with:
  - Severity of coronary atherosclerosis
  - Subsequent major adverse cardiovascular events and death
  - Type 2 diabetes/insulin resistance
  - Obesity
  - Smoking
  - Oral estrogens

Levels of hsCRP[121]	
<1 mg/L	Low systemic inflammatory status, low vascular risk
1-3 mg/L	Moderate vascular risk
>3 mg/L	Higher vascular risk in context of other risk factors
>10 mg/L	Unspecified inflammation; may reflect transient infection or other acute phase response; repeat in 2-3 weeks

Badimon L, et al. *Front Immunol*. 2018;9:430.
Adukauskienė D, et al. *Medicina*. 2016;52(1):1-10.
Ridker PM. *JACC*. 2016;67(6):712-723.
Assadpour Piranfar M. *Int Cardiovasc Res J*. 2014;8(1):6-8.

High-sensitivity C-Reactive Protein (hsCRP)

- hsCRP is a **modifiable** risk factor for cardiovascular disease
  - Foods
    - Extra virgin olive oil
    - Omega-3 fatty acids
    - Low glycemic index foods
    - Fiber
  - Lifestyle
    - Exercise
    - Weight reduction
    - Smoking cessation
  - Medications
    - Aspirin

Souza PAL, et al. *Nutrients*. 2017;9(10).
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Kianoush S, et al. *JAHA*. 2017;6(6).
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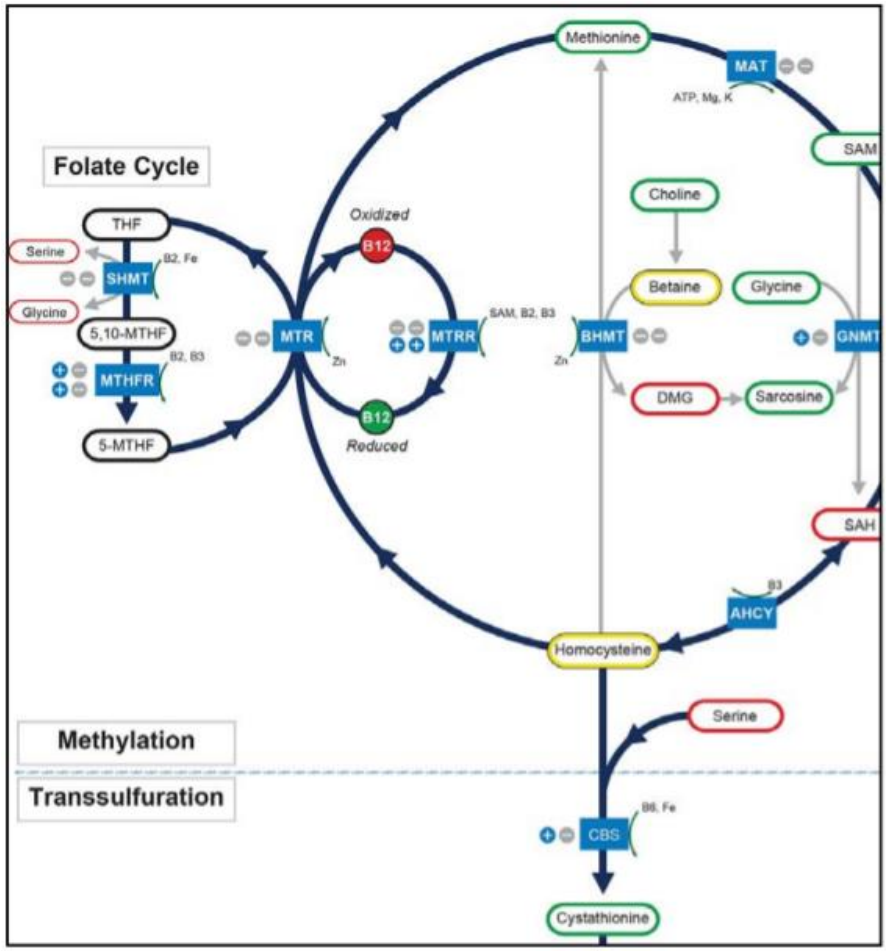
Homocysteine

- Risk factor for non-coronary atherosclerosis and coronary artery disease
  - Toxic to endothelium, prothrombotic, increases collagen production, and decreases availability of nitric oxide
- Elevated levels are associated with:
  - Atherosclerosis and coronary artery disease
  - Osteopenia
  - Neurodegenerative conditions
  - Mood disorders
  - IBD and colon cancer risk

Castro R, et al. *J Inherit Met Dis.* 2006;29(1):3-20.
Oussalah A, et al. *Aliment Pharmacol Ther.* 2011;34(10):1173-84.
Behera J, et al. *J Cell Phys.* 2017;232(10):2704-09.
Gariballa S. *Age Ageing*. 2011;40(6):702-05.

Homocysteine

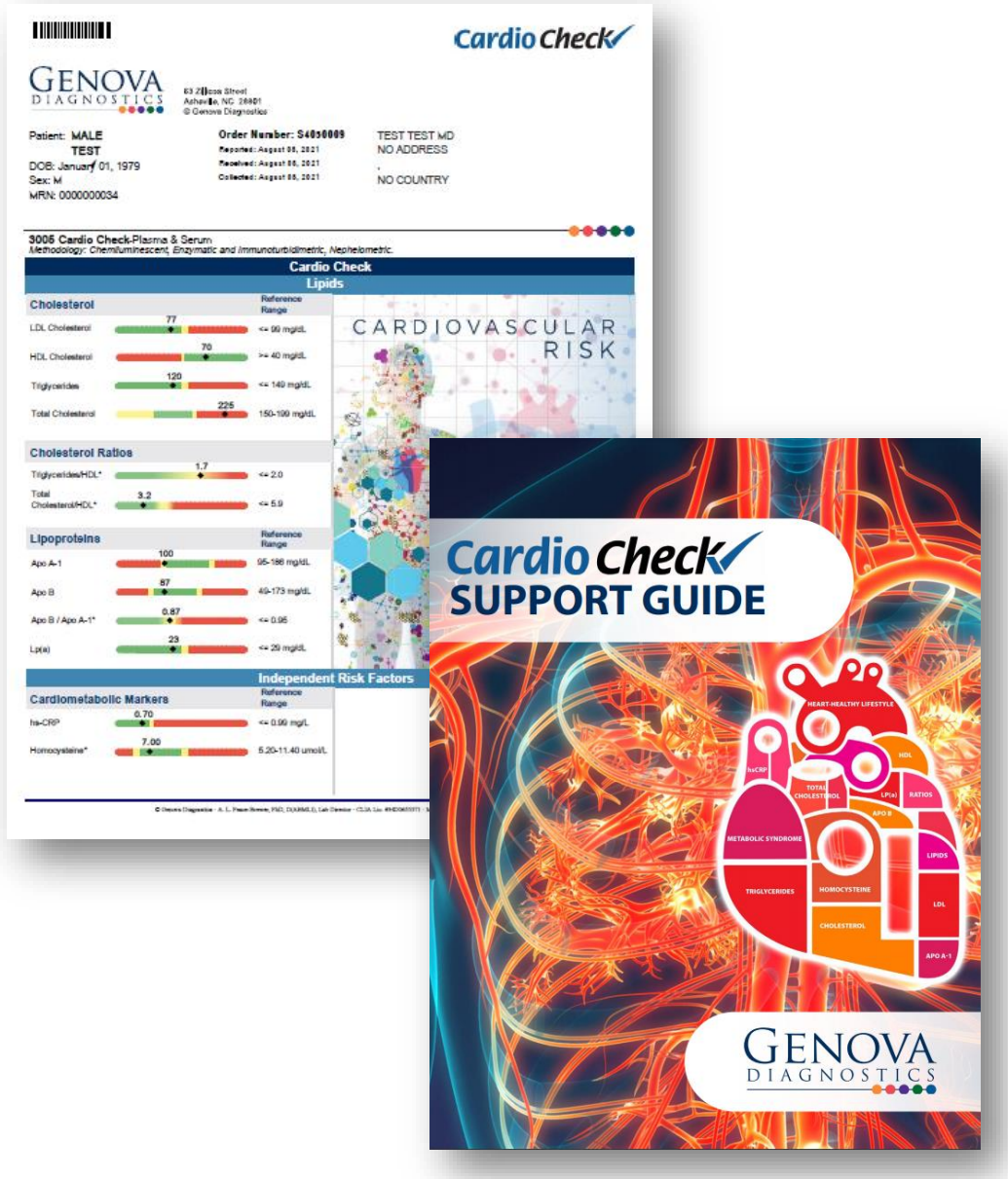
- Homocysteine is a **modifiable** risk factor for cardiovascular disease
  - Nutrients
    - B-vitamins: 6/9 (5-MTHF)/12 (activated)
    - Iron
    - Choline
    - SAMe



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Key Takeaways

- Advanced blood assessment of lipids and cardiometabolic analytes providing insight into cardiovascular risk
  - Conventional Biomarkers: LDL, HDL, TG, and TC
  - Novel Biomarkers: Apo A-1, ApoB, Lp(a), hsCRP, and HCY
- Cardio Check Support Guide
  - Description of biomarkers
  - **Heart-Healthy Lifestyle** section with diet and lifestyle guidance
  - Links to additional educational resources



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Presenter:
Lahnor Powell, ND, MPH

US Client Services: 800-522-4762

UK Client Services: 020.8336.7750

We look forward to hearing from you!

Questions?

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Cardio Check

An Advanced Assessment of Cardiovascular and Metabolic Risk

Lahnor Powell, ND, MPH

Atlanta Medical Education Specialist | Department of Medical Affairs | Genova Diagnostics

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