



# Overview of Direct-to-Consumer Testing from the Hospital Laboratory Perspective

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# Disclosure

- Nothing to disclose

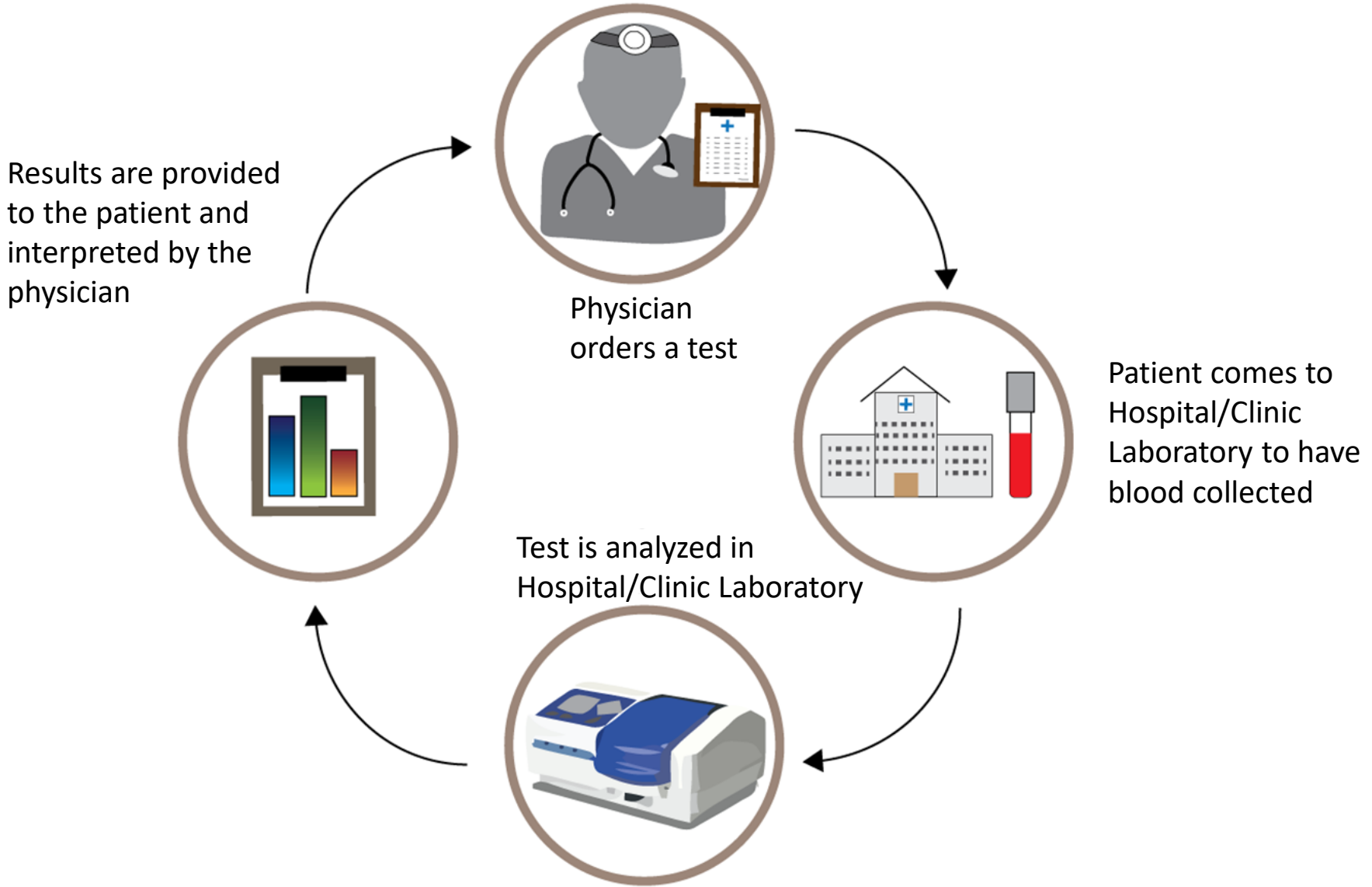


# Learning Objectives

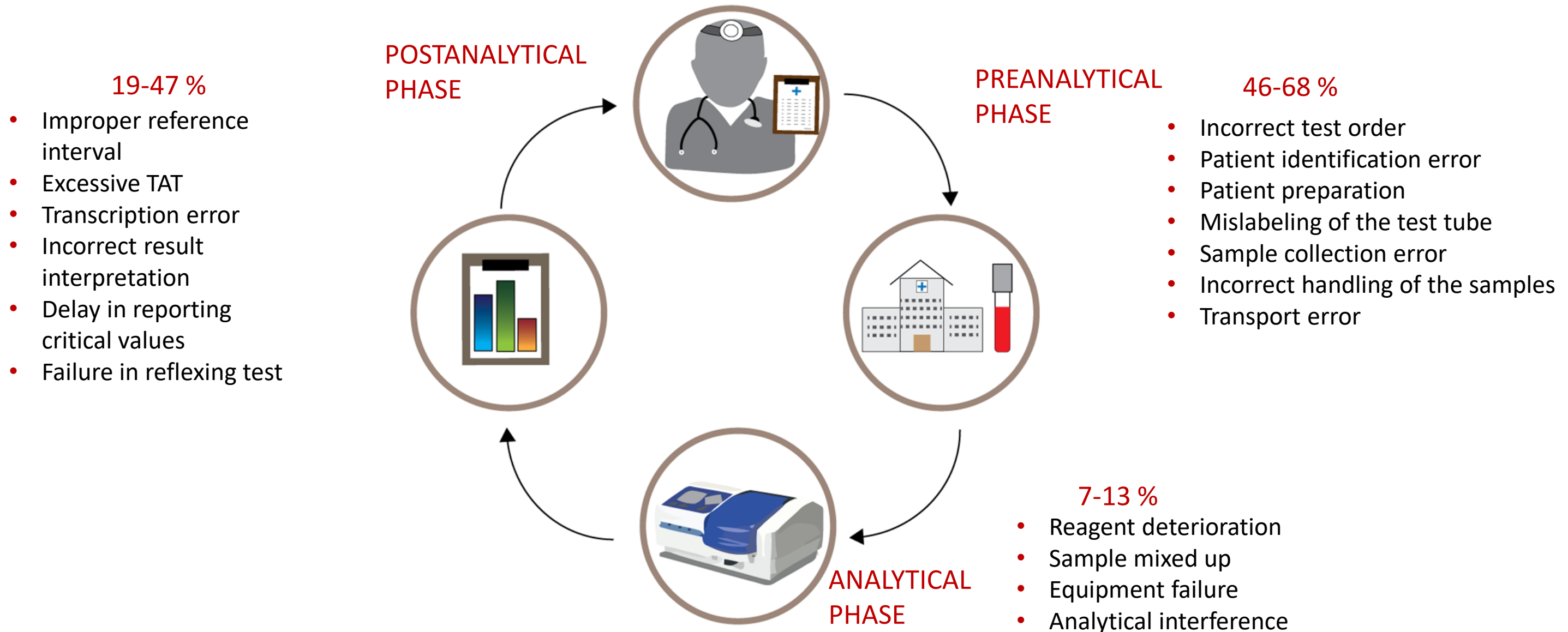
- Describe different types of DTC testing
- Compare DTC tests to tests performed in the traditional hospital setting from a quality perspective
- Identify benefits and limitations of DTC testing
- Discuss what laboratory professionals can do to support safe and effective DTC testing to the general public



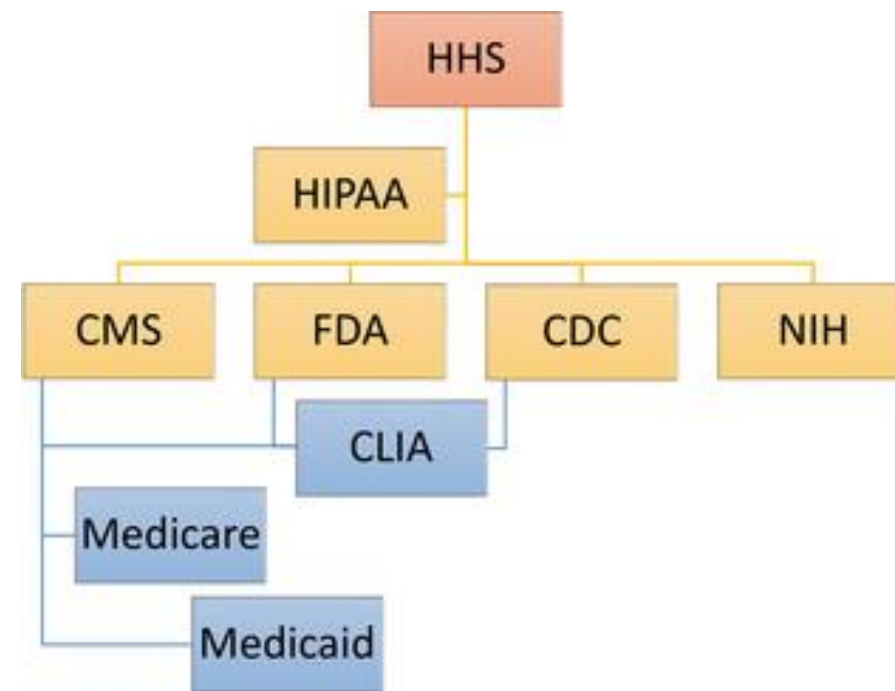
# Hospital/Clinic lab testing- brain to brain loop



# Error sources and error rate



# Regulatory oversight of Laboratory Testing



NATIONAL ARCHIVES Code of Federal Regulations A point in time eCFR system

Title 42

Displaying title 42, up to date as of 9/08/2022. Title 42 was last amended 8/29/2022. view historical versions

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EDFR CONTENT

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**PART 493 - LABORATORY REQUIREMENTS**

**Authority:** 42 U.S.C. 263a, 1302, 1395x(e), the sentence following 1395x(s)(11) through 1395x(s)(16).

**Source:** 55 FR 9576, Mar. 14, 1990, unless otherwise noted.

**Subpart A - General Provisions**

**Source:** 57 FR 7139, Feb. 28, 1992, unless otherwise noted.

**§ 493.1 Basis and scope.**

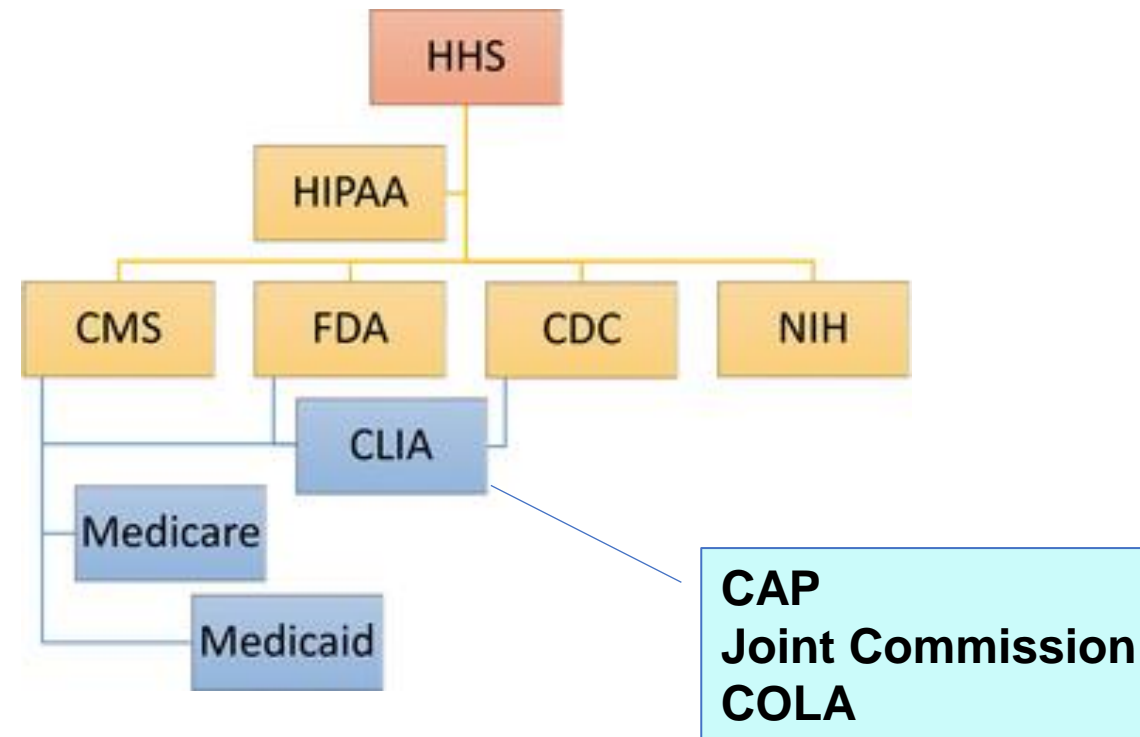
This part sets forth the conditions that all laboratories must meet to be certified to perform testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). It implements sections 1861(e) and (j), the sentence following section 1861(s)(13), and 1902(a)(9) of the Social Security Act, and section 353 of the Public Health Service Act, as amended by section 2 of the Taking Essential Steps for Testing Act of 2012. This part applies to all laboratories as defined under "laboratory" in § 493.2 of this part. This part also applies to laboratories seeking payment under the Medicare and Medicaid programs. The requirements are the same for Medicare approval as for CLIA certification.

- Laboratory according to CLIA (Clinical Laboratory Improvement Amendments):  
*Any facility that examines human specimens for the diagnosis, prevention, or treatment of any disease or impairment of or the assessment of the health of human beings*

[https://www.ecfr.gov/current/title-42/chapter-IV/subchapter-G/part-493#p-493.15\(c\)](https://www.ecfr.gov/current/title-42/chapter-IV/subchapter-G/part-493#p-493.15(c))



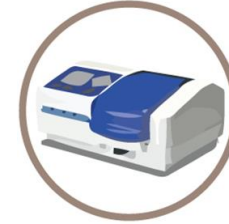
# What is the role of Accrediting Bodies?



- Accreditation organizations (CAP) enforces CLIA laws
- CAP provides oversight and assistance with quality of laboratory medicine



# How Clinical Laboratory ensures quality?



Across test system:

Statistical quality control

Proficiency testing

Method validation

Quality indicators



In a sample:

HIL indices

Delta checks

Running a sample in duplicate

Implausible values

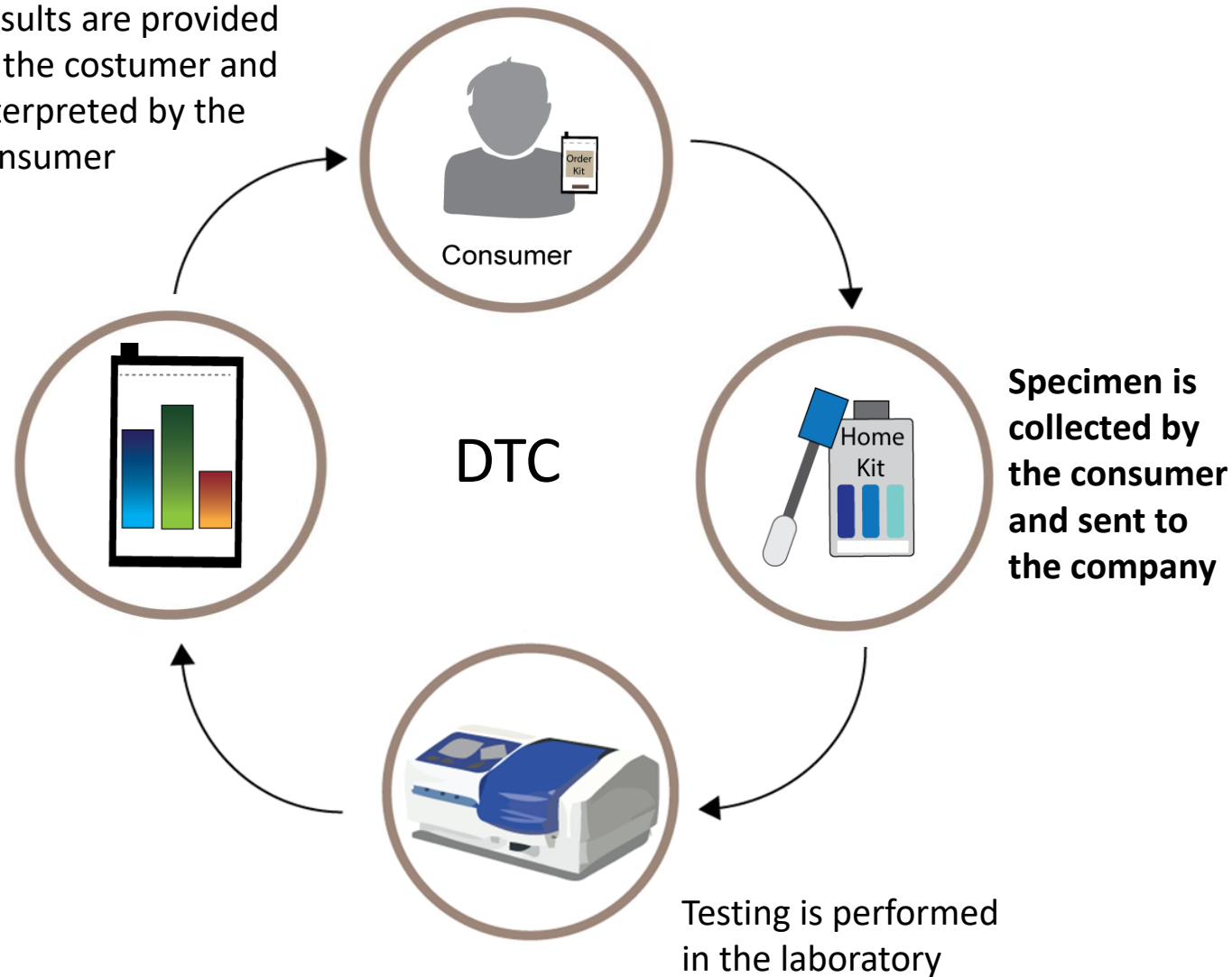
- HIL: hemolysis, icteric and lipemia
- Delta checks: comparison of laboratory test results with results obtained on previous samples from the same patient



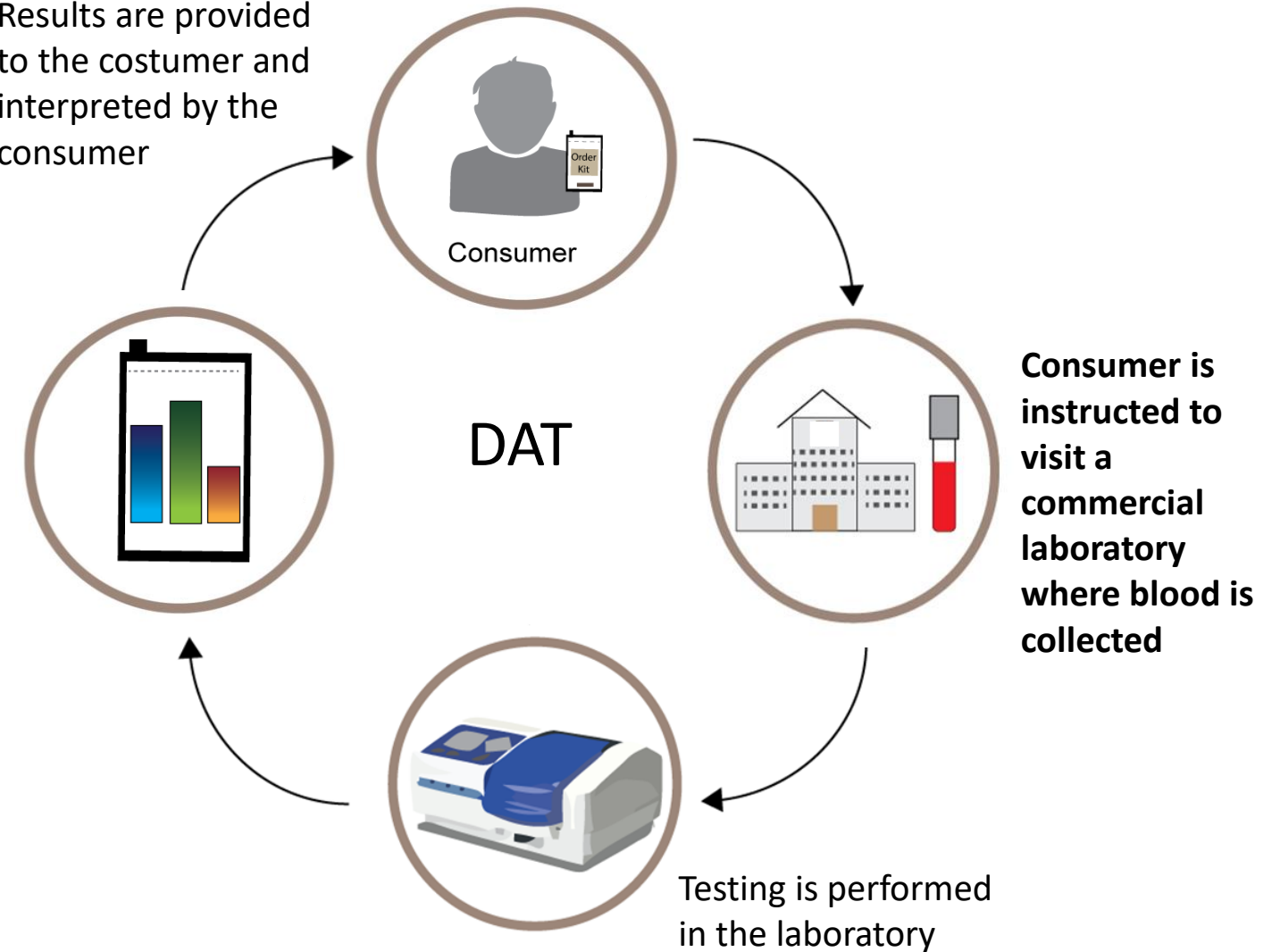


# DTCT versus DAT (direct access) testing

Results are provided to the customer and interpreted by the consumer



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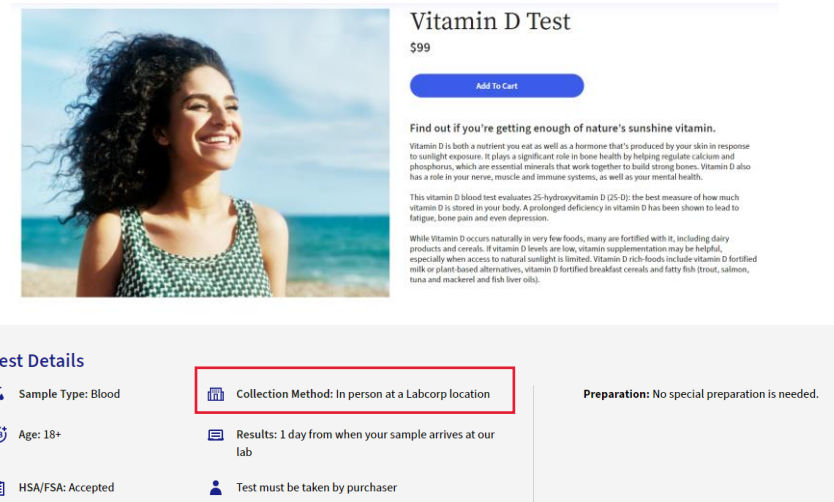
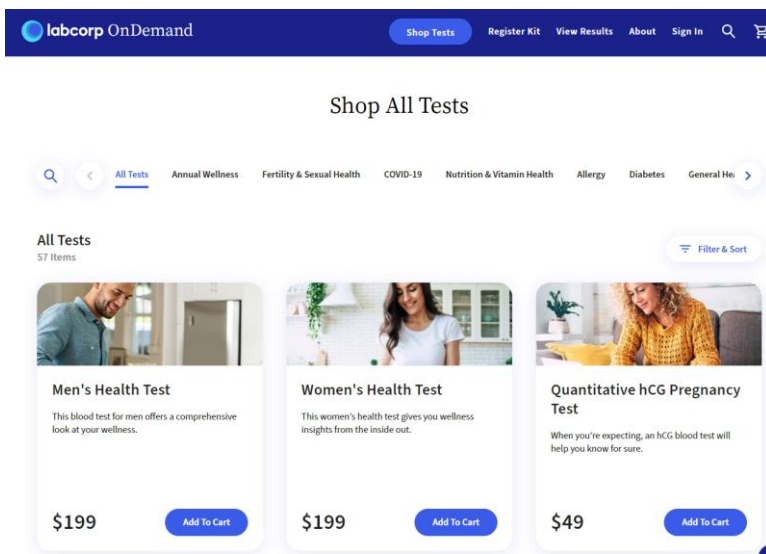
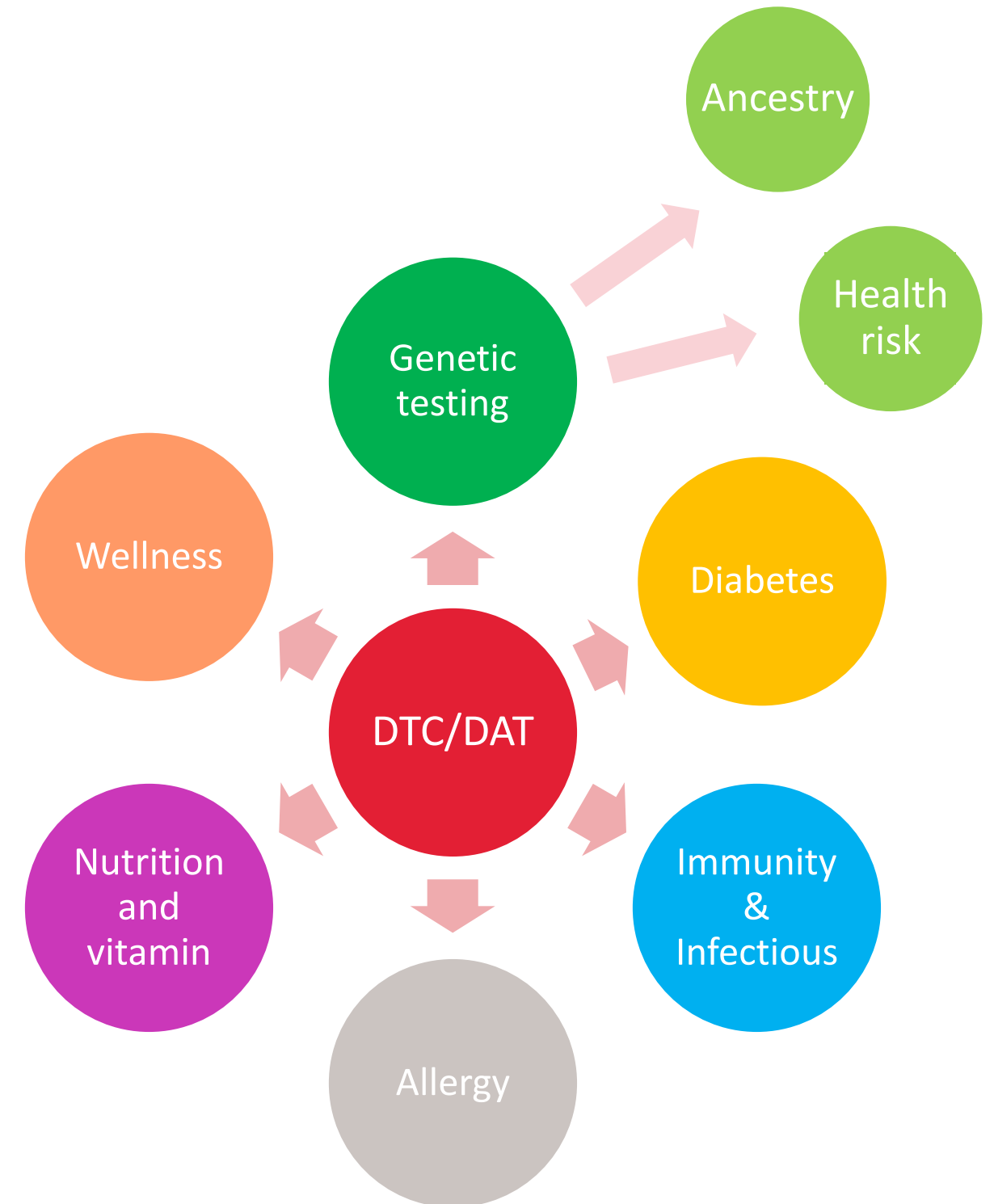


# Types of DTCT/DAT?

- Information available online:

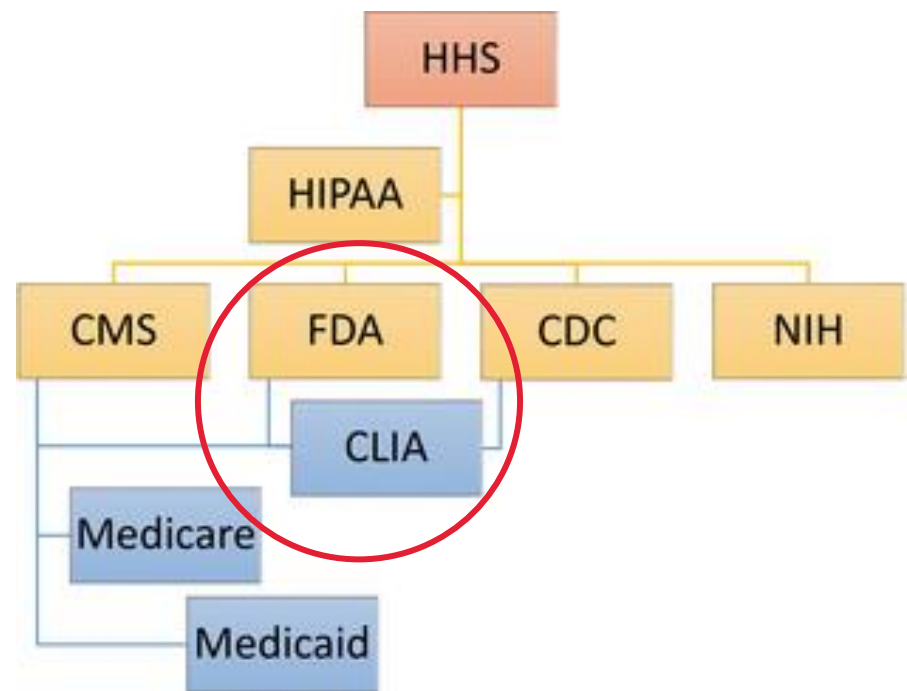
[Explore Our Lab Tests | Labcorp OnDemand](#)

[Order Your Own Lab Tests & Blood Tests Online | Quest® \(questhealth.com\)](#)



# Government Oversight of DTCT/DAT

- In the US, DTC lab testing is regulated at the federal and state levels



- States permitted to perform DAT: AK, AR, DE, DC, IN, IA, KS, LA, MN, MS, MO, MT, NE, NM, NC, ND, OH, OK, SD, UT, VT, WA, WV, WI, TX, VA,
- States with some limits on DAT: AZ, CA, CO, FL, IL, ME, MD, MA, NV, NJ, OR, NY.
- States where DAT is prohibited: AL, CT, GA, HI, ID, IA, KY, MI, NH, PA, RI, SC, TN, WY.

- FDA reviews tests for moderate to high-risk medical purposes (23andme – health predisposition, pharmacogenetics, carrier status) but does not review wellness, ancestry or low risk
- Federal Trade Commission (FTC) - investigates deceptive marketing practices and false claims



# CAP checklist

## Laboratory General Checklist

CAP Accreditation Program



### DIRECT-TO-CONSUMER TESTING

*NOTE: Direct-to-consumer (DTC) tests are defined as tests that are requested or ordered by the consumer. It is also commonly referred to as "direct access testing" or "consumer initiated testing."*

*All applicable requirements in other areas of the checklists apply to direct-to-consumer testing. This checklist section applies only to laboratories subject to US regulations. This checklist section does not apply to health fairs.*

#### Inspector Instructions:



- Direct-to-consumer testing policies and procedures
- Sampling of direct-to-consumer laboratory reports

#### GEN.41460 DTC Jurisdiction Phase II



**The laboratory performs DTC testing and reports results of DTC tests only in jurisdictions where such testing is lawful.**

*NOTE: No less than every two years, the laboratory must verify which jurisdictions permit DTC testing if it provides direct-to-consumer testing. The scope of testing performed must be limited to those allowed under the applicable law.*

##### Evidence of Compliance:

- ✓ Record that the laboratory has reviewed applicable laws/regulations

#### GEN.41475 DTC Report Phase II

**The test report includes test results, reference intervals, interpretation as applicable, and limitations of the test, as applicable, in language readily understandable by a lay person.**

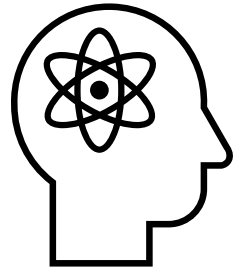
#### GEN.41485 DTC Report Phase II

**The test report includes information that helps the consumer to contact a licensed health care professional about the clinical significance of the test result.**

*NOTE: This information may consist of the name, phone number, and email address of a health care professional. Alternatively, it may be the phone number of an office at the laboratory or medical center or website that can provide contact information to the consumer.*



# Advantages of DTCT/DAT



**Self-empowerment**

**Convenience**

**Accessibility**

**Avoiding discrimination (STD)**

**Affordability (transparent pricing)**

**Non-invasive tests (saliva)**



# Limitations of DTCT/DAT



**Result  
interpretation**

**Problem of  
scientific literacy**

**Training of  
physicians in  
genetics**

**Over-use or  
inappropriate use  
of tests**

**Burden to the  
healthcare system**

**Privacy concerns**

**Reliability of the  
results**

**Lack of FDA  
oversight**





# Currently, FDA does not review laboratory developed test

- If the single laboratory created and performed the test, FDA does not review these tests
- FDA proposed a rule to regulate laboratory developed tests with the support of CMS and CAP
- Theranos Scandal:
  - 900,000 patient results which were subsequently voided
  - CLIA certificate, but their assays were treated as LDT (no FDA oversight)
  - Only 1 FDA approved test- herpes simplex virus out of 200 promised tests
  - No CAP accreditation
  - CMS inspection revealed issues with:
    - Quality management system (QC and PT)
    - Accuracy of patient results
    - Missing competencies on laboratory personnel



# ADLM Position

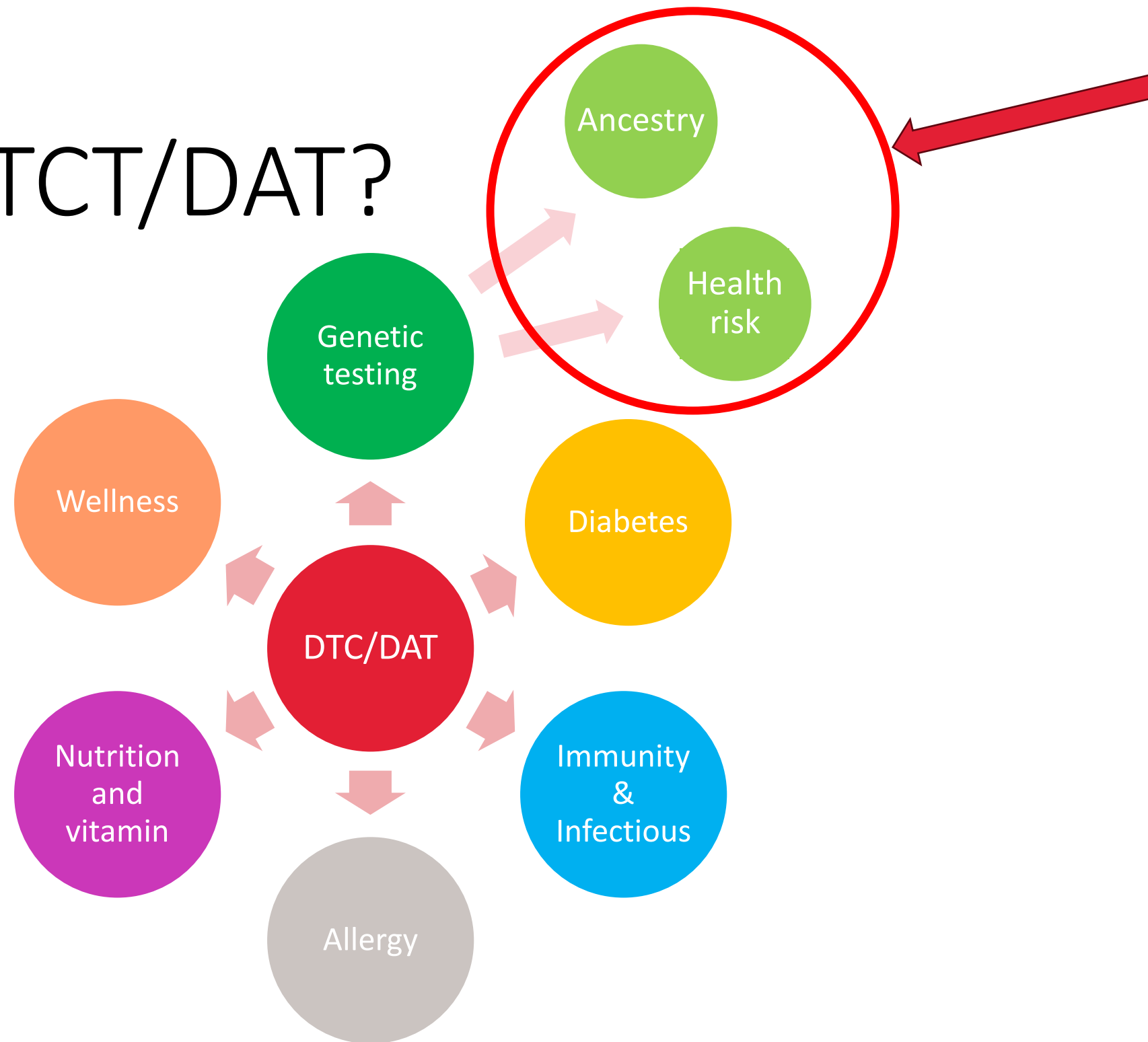
- Supports DTC laboratory testing services that have demonstrated analytical and clinical validity and utility
- Recommends that only CLIA-certified laboratories perform DTC testing with sufficient information provided to the consumers
- Supports Federal Trade Commission (FTC) enforcement against DTC providers engaging in false and misleading marketing practices
- Urges CMS and FDA to ensure DTC providers disclose sufficient information about their products
- Encourages evaluating test results as part of an overall health assessment with healthcare provider

<https://www.myadlm.org/advocacy-and-outreach/position-statements/2019/direct-to-consumer-laboratory-testing>





# Types of DTCT/DAT?



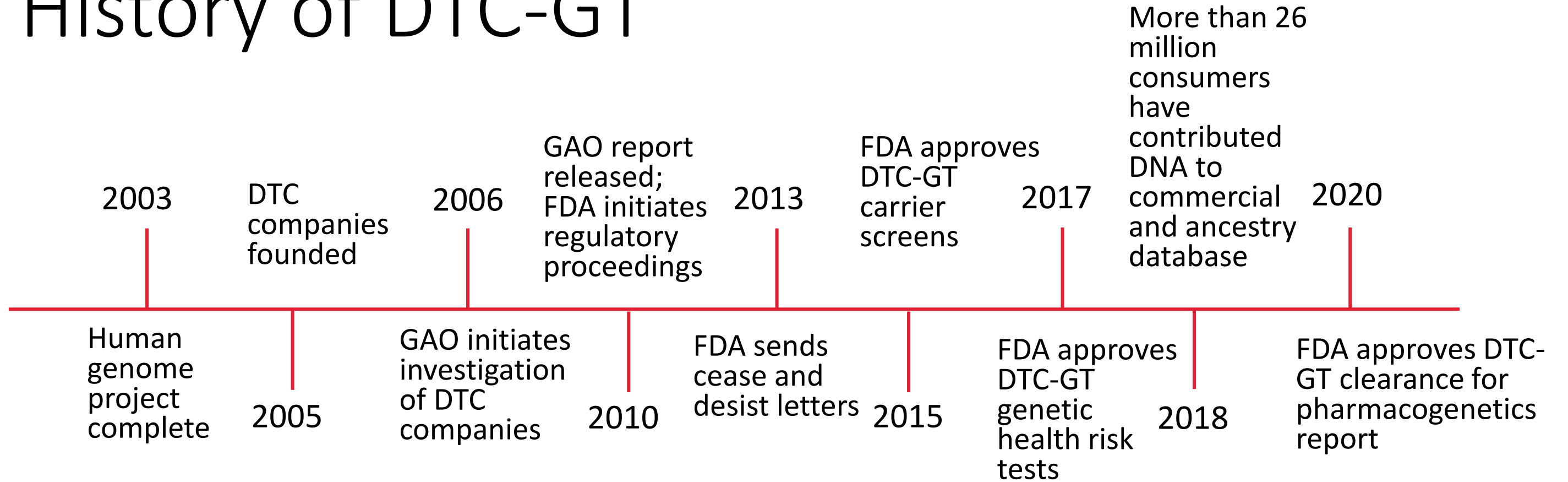
# DTC- Genetic Testing

- Growing rapidly due to large decrease in sequencing costs and increasing public data on human genetic variation (in 2018, 26 million consumers)
- Testing options:
  - **Ancestry:** 23andMe, Ancestry.com, Family Tree DNA...
  - **Health Conditions:** 23andMe, Veritas
  - **Fitness and Athletic Performance:** CircleDNA, Fitness Genes, simplified Genetics...
- Several countries in Europe (e.g. France and Germany) banned DTC-GT
- **Not used to diagnose**
- **Genetic counselling** is important for result interpretation

 ancestry



# History of DTC-GT



**Contradictory Risk Predictions for Prostate Cancer and Hypertension**

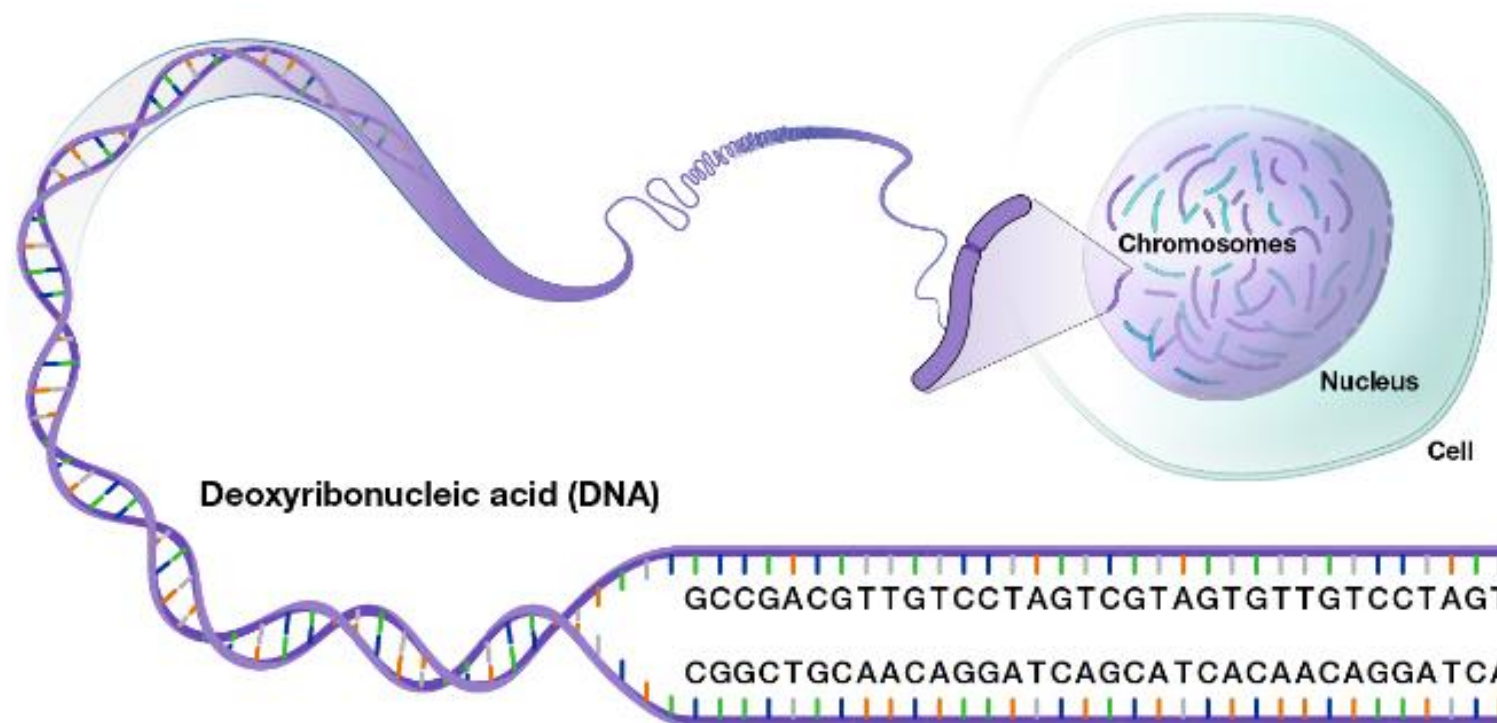
Gender	Age	Condition	Company 1	Company 2	Company 3	Company 4
Male	48	Prostate cancer	Average	Average	Below average	Above average
		Hypertension	Average	Below average	Above average	Not tested

Source: GAO.

GAO: government accountability office

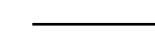


# Single Nucleotide Polymorphisms (SNPs)



Common genotype

```
TTGTCCTAGTCGTAGTGTGT  
AACAGGATCAGCATCACAACA
```

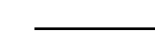


No effect on protein function

Variant genotype

Person 1

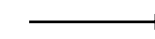
```
TTGTCCTAGGCGTAGTGTGT  
AACAGGATCCGCATCACAACA
```



No effect on protein function

Person 2

```
TTGTCCTAGGCGTAGTGTGT  
AACAGGATCCGCATCACAACA
```

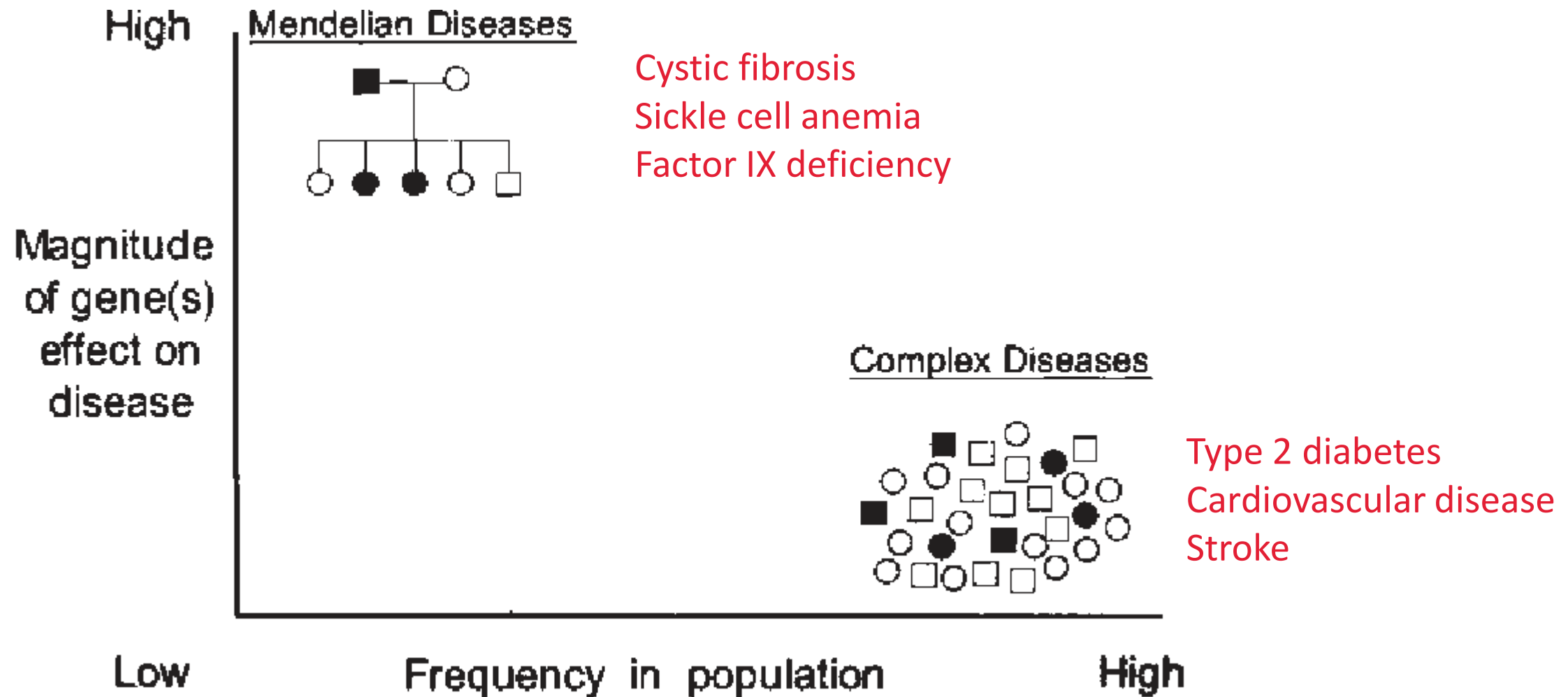


Negative effect on protein function

<https://www.genome.gov/about-genomics/educational-resources/fact-sheets/human-genomic-variation>



# Complex versus Mendelian Diseases



Juran et al. Applying genomics to the study of complex disease. Semin Liver Dis. 2007 Feb;27(1):3-12



# Sequencing vs. Genotyping Technology

## Sequencing

**DNA Sequence**

TTAGACTAGAGC	CCAAGGAAAT
GGGGCTGTTGAC	AACTATTATA
GTTTGGGGTGA	TGTCGGCGATG
ATAAATTATTGT	GTAATAATTAA
ACAATCCTTCAAC	TTATATTGTTA
GTGCCCCACGG	TCAATATAGTATTT
TGGCACCTGA	AAATCGTGTA AAA
GGAGGGGCACA	AAAATATATATTT

402 403

- Known and unknown variants
- Method used by clinical labs

## Genotyping

**DNA Sequence 1**

TTAGACTAGAGC  
GGGGCTGTTGAC  
GTTTGGGGTGA  
ATAAATTATTGT  
ACAATCCTTCAAC  
GTGCCCCACGG  
TGGCACCTGA  
GGAGGGGCACA

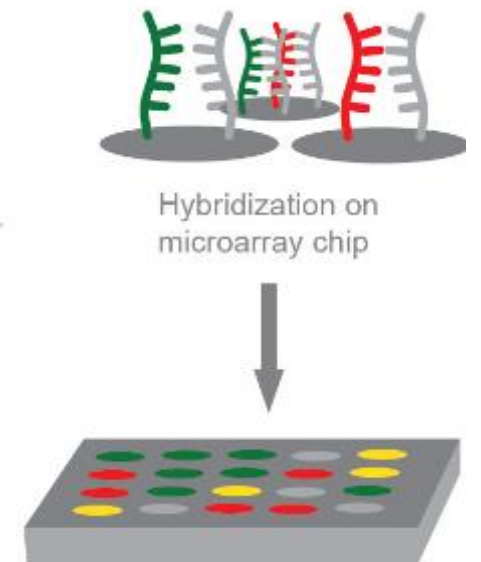
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**DNA Sequence 2**

TTAGACTAGAGC  
GGGGCTGTTGAC  
GTTTGGGGTGA  
ATAAATTATTGT  
ACGCCCTTCAAC  
GTGCCCCACGG  
TGGCACCTGA  
GGAGGGGCACA

402

- Known variants
- DTC-GT



<https://goldbio.com/articles/article/Types-of-PCR-used-for-Genetic-Research>



# FDA-Authorized DTC Genetic Tests

## Genetic Health Risk Test

- BRCA1/BRCA2 (selected variants)
- Hereditary Thrombophilia
- Alpha-1 Antitrypsin Deficiency
- Late-onset Alzheimer's Disease
- Parkinson Disease
- Gaucher Disease Type 1
- Factor XI Deficiency
- Celiac Disease
- Glucose-6-Phosphate-Dehydrogenase Deficiency
- Hereditary Hemochromatosis
- Early-Onset Primary Dystonia

## Pharmacogenetic

### Gene Variants

- CYP2C19\*2, \*3, \*17
- CYP2C9 \*2, \*3, \*5, \*6
- CYP3A5 \*3
- UGT1A1 \*6, \*28
- DPYD \*2A
- TPMT \*2, \*3C
- SLCO1B1\*5
- CYP2D6 \*2, \*3 ....

## Carrier Screening

- Bloom syndrome

<https://www.fda.gov/medical-devices/in-vitro-diagnostics/direct-consumer-tests#list>





# Non-FDA-Authorized DTC Genetic Tests

## Genetic Health Risk Test

- Type 2 Diabetes
- Skin cancer (Melanoma)
- Anxiety
- Coronary Artery Disease
- Gallstones
- LDL Cholesterol
- Panic Attacks
- High blood pressure
- Nonalcoholic Fatty Liver disease
- Kidney Stones
- Migraine
- .....

## Pharmacogenetic

## Carrier Screening

- Cystic fibrosis
- Sickle Cell anemia
- Glycogen Storage Disease
- Limb-Girdle Muscular Dystrophy
- Hereditary Fructose Intolerance
- D-Bifunctional Protein Deficiency
- Maple Syrup Urine Disease
- Fanconi Anemia Group C
- .....





# What do DTC-GT results mean?



- Genetic variant detected-  
not likely increased risk/increased risk
- Genetic result is associated with  
increase likelihood of X
- Positive carrier result-  
pass this variant to your children
- Genetic variant NOT detected  
(still could have a variant not covered by  
this test) **does not mean no risk**
- Genetic variant NOT detected
  - Sickle cell anemia



- Caused by the variant in this report
- Caused by variants in other genes **not in this report**
- Caused by other factors **not in this report**



**34 out of 100** diagnosed with X  
**66 out of 100** no diagnosis of X



# Professional organizations on DTC-GT



*“Due to the complexities of genetic testing and counseling, the **self-ordering of genetic tests** by patients over the telephone or the Internet, and their use of genetic “home testing” kits, is **potentially harmful**. Potential harms include inappropriate test utilization, misinterpretation of test results, lack of necessary follow-up, and other adverse consequences.”*

*“NSGC advises consumers **to consider the risks, limitations, and psychological implications** of genetic testing for themselves and their families before purchasing an at-home genetic test.... Results obtained through DTC-GT should be **reviewed with a genetics specialist**, as some findings may need to be **confirmed in a clinical laboratory** before being used in healthcare decision-making”*



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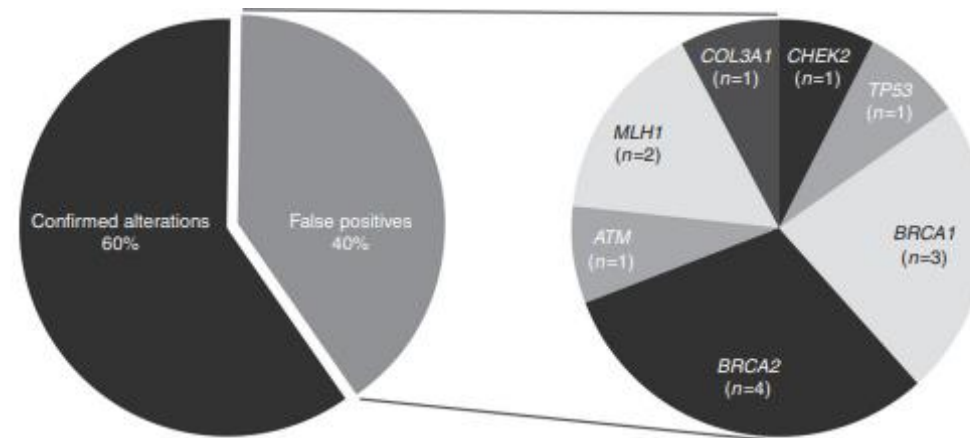
*“NSGC advises consumers **to consider the risks, limitations, and psychological implications** of genetic testing for themselves and their families before purchasing an at-home genetic test.... Results obtained through DTC-GT should be **reviewed with a genetics specialist**, as some findings may need to be **confirmed in a clinical laboratory** before being used in healthcare decision-making”*

**Quality:** concern with **analytical** and **clinical** validity

**Claims:** may in some cases be **exaggerated** or **unsupported** by scientific evidence



# High rate of False Positives in DTCT-GT



**Figure 1 False-positive variants in clinically actionable genes.** The pie chart on the left indicates of the variants analyzed, 60% were confirmed and 40% were false positives. The pie chart on the right shows which genes were involved with the false-positive cases and how often those false calls were detected in this study.

**Table 3 Classification discrepancies**

Gene	Variant	DTC/third party <sup>a</sup>	Ambry <sup>b</sup>	ClinVar <sup>c</sup>	ESP <sup>d</sup>	1000 Genomes <sup>e</sup>	dbSNP <sup>f</sup>
ATM	p.M1040V (c.3118A > G)	Increased risk	Benign	Benign	1.36%	0.95%	1.48%
BRCA1	p.Q356R (c.1067A > G)	Increased risk	Benign	Benign	4.59%	2.81%	3.97%
BRCA2	p.N372H (c.1114A > C)	Increased risk	Benign	Benign	23.32%	24.26%	24.44%
COL3A1	p.A698T (c.2092G > A)	Increased risk	Benign	Benign	21.39%	21.16%	19.16%
COL5A1	c.655-8689C > T	Increased risk	Deep intronic—benign	N/A	N/A	N/A	N/A
COL5A1	c.654+2749A > G	Increased risk	Deep intronic—benign	N/A	N/A	N/A	N/A
COL5A1	c.1827+399C > T	Increased risk	Deep intronic—VUS	N/A	N/A	N/A	N/A
COL5A1	c.1827+1142T > C	Increased risk	Deep intronic—benign	N/A	N/A	N/A	N/A

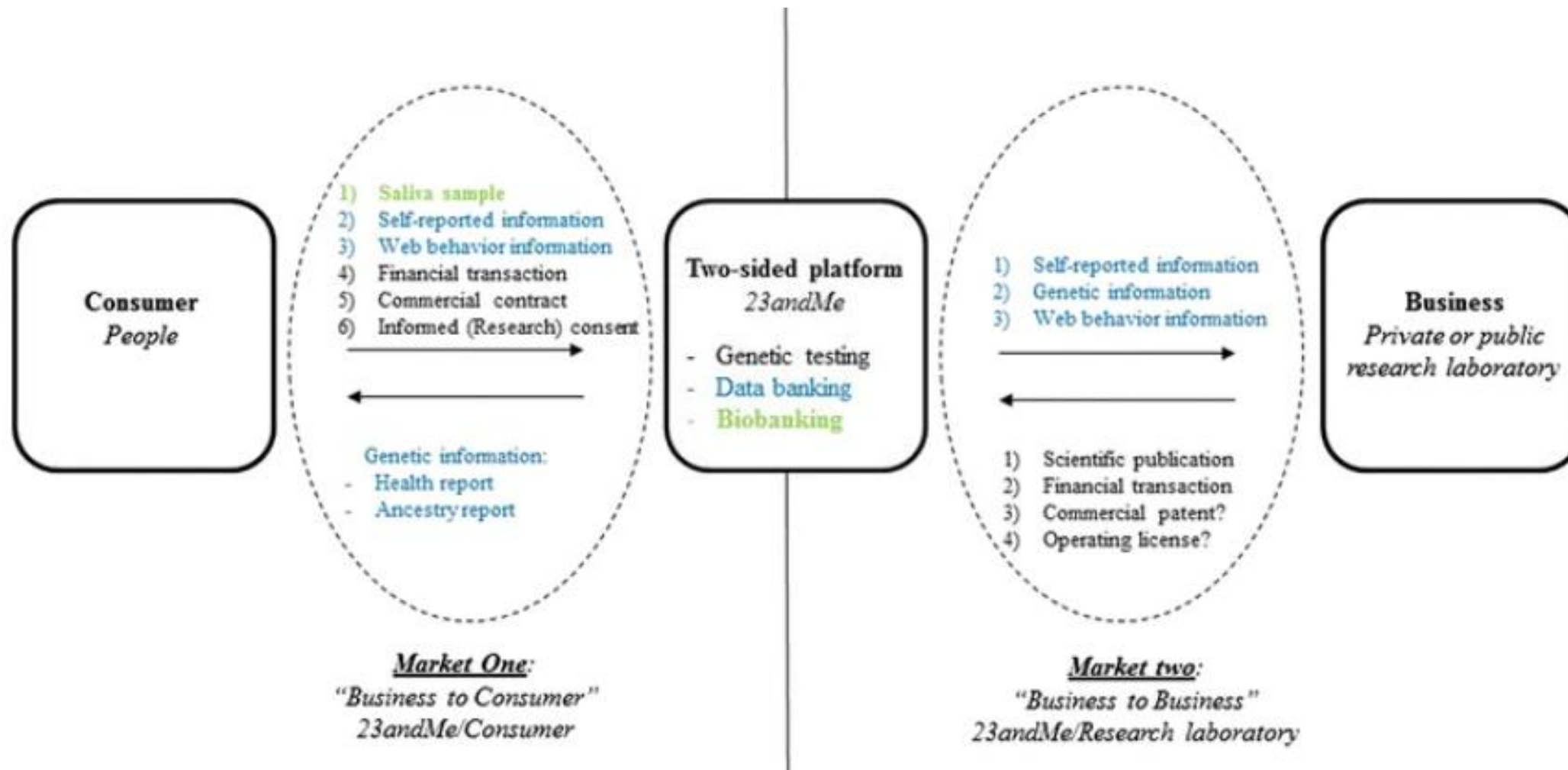
DTC, direct to consumer; N/A, not available; VUS, variant of unknown significance.

<sup>a</sup>Variant classification provided by the DTC company or a third-party interpretation service. <sup>b</sup>Variant classification provided by Ambry. <sup>c</sup>Variant classification provided in ClinVar (clinical laboratory submissions only). <sup>d</sup>Exome Sequencing Project population frequency database. <sup>e</sup>1000 Genomes population frequency database. <sup>f</sup>dbSNP population frequency database.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6301953/>



# 23andMe two-sided market model



Stoekle et al. 23andMe: a new two-sided data-banking market model. BMC Medical Ethics. 2016.





# 2020 Consumer reports survey

- 2000 U.S. adults were surveyed regarding DTC-GT
  - 20% taken a DTC-GT: *ancestry, general curiosity or as a gift*
  - 80% did not take the DTC-GT due to: *no interest, too expensive, worries about the privacy of data*

- *Believe in the results:*

How accurate do you believe the results of home genetic tests are?	
	Total
	%
Very inaccurate	5
Somewhat inaccurate	16
Somewhat accurate	61
Very accurate	18
Base: All respondents	
	1,972

- Understanding of privacy

Federal medical privacy laws, such as HIPAA, protect the results of commercial home genetic tests. Is this true or false?	
	Total
	%
True	52
False	48
Base: All respondents	
	1,985

Genetic information collected by home genetic testing companies cannot legally be shared with other companies, such as life insurance companies. Is this true or false?	
	Total
	%
True	60
False	40
Base: All respondents	
	1,994



# Personal experience



## PROS

- Educational experience
- Data and report well presented
- Easy to collect the specimen

## CONS

- Lots of questions to answer in the questionnaire
- 50% confidence interval
- Reference range
- Long time to get the results/anxiety
- Needed the input from the professional



# Wellness and Trait reports

## Wellness report

- Alcohol flush reaction
- Caffeine Consumption
- Cat/Dog allergy
- Deep sleep
- Genetic weight
- Lactose intolerance
- Muscle composition
- Nearsightedness
- Saturated fat and weight
- Seasonal allergies
- Sleep movement

## Trait reports

- Ability to match musical pitch
- Asparagus odor detection
- Bitter taste
- Bunions
- Cheek dimples
- Cilantro taste aversion
- Cleft chin
- Dandruff
- Earlobe type
- Eye color
- **Fear of heights**
- Fear of public speaking
- Finger length ratio
- Flat feet
- Freckles

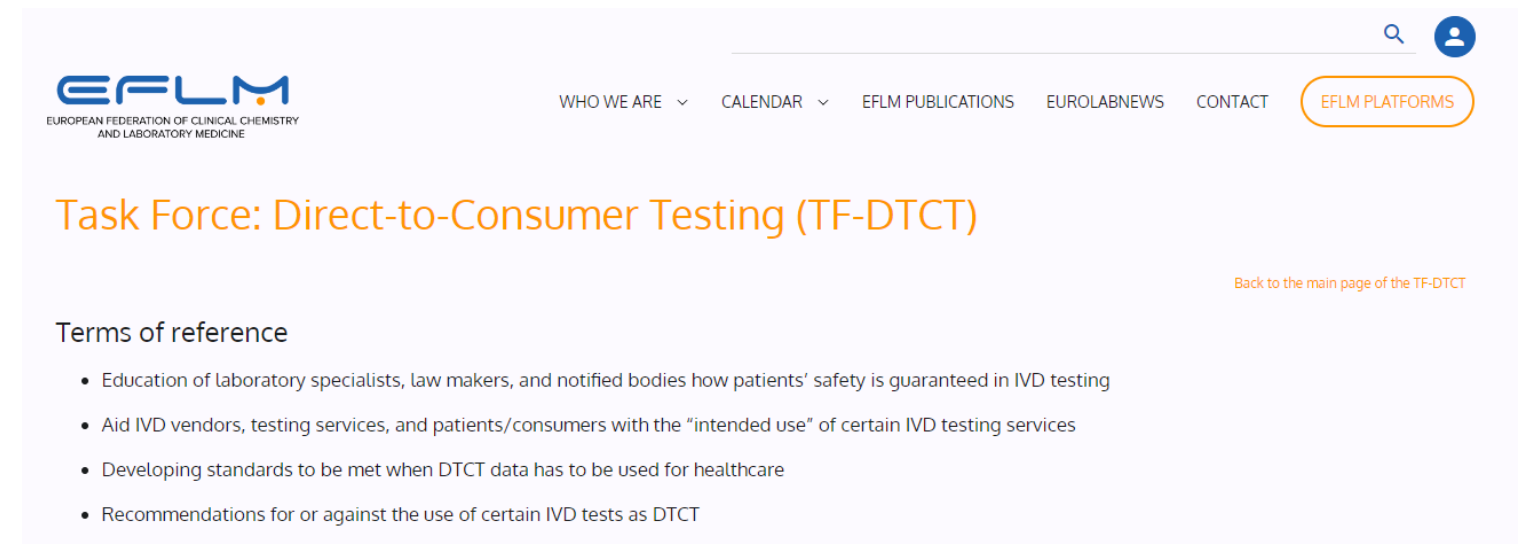
- Hair photobleaching
- Hair texture
- Hair thickness
- **Ice cream flavor preference**
- Light or dark hair
- Misophonia
- **Mosquito bite frequency**
- Motion sickness
- Newborn hair
- Photic sneeze reflex
- Red hair
- Skin pigmentation
- Stretch marks
- **Sweet vs salty**
- Toe length ratio
- Unibrow
- **Wake-up time**
- Widow's peak





# How can laboratory professional support DTCT/DAT?

- Educational initiatives (conference, webinars, involvement with publishing the studies)
- <https://labtestsonline.org/>
- <https://www.genome.gov/For-Health-Professionals/Provider-Genomics-Education-Resources/Healthcare-Provider-Direct-to-Consumer-Genetic-Testing-FAQ>
- European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) efforts:



<https://www.eflm.eu/site/who-we-are/task-forces/tf-direct-to-consumer-testing>



# Summary

- DTCT/DAT can have clinical utility
- False positive results do exist so interpret results with caution
- Genetic testing should be interpreted by genetic counselor
- Accredited laboratories are key to ensuring quality
- FDA-authorized tests have good analytical and clinical validity but variable clinical utility
- Be aware that some claims made regarding DTC-GT can be exaggerated or unsupported by scientific evidence
- Big Thanks to **Dr. Iyare Izevbaye** – molecular pathologist from Emory University and **Dr. Molly Accola** – senior laboratory development specialist in molecular pathology lab at UWHealth in Madison WI



(Image credit: alexkich / Shutterstock)





Thank you!

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