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The efficiency of several one-step testing strategies for the diagnosis of hepatitis C

Javier Crespo[1], José María Eiros-Bouza[2], Antonio Javier Blasco-Bravo[3], Pablo Lázaro-de-Mercado[3], Antonio Aguilera-Guirao[4], Federico García[5], Javier García-Samaniego-Rey[6] and José Luis Calleja-Panero[7]

[1]Digestive Unit. Marqués de Valdecilla University Hospital. IDIVAL. School of Medicine. University of Cantabria. Santander, Spain. [2]Microbiology Department. Hospital Universitario Río Hortega. Valladolid, Spain. [3]Independent Health Services Researcher. Madrid, Spain. [4]Microbiology Department. Complejo Hospitalario Universitario de Santiago de Compostela. Xerencia de Xestión Integrada de Santiago. Santiago de Compostela. A Coruña, Spain. [5]Clinical Microbiology Department. Hospital Universitario San Cecilio. Instituto Investigación Biosanitaria Ibs. Granada, Spain. [6]Digestive Unit. Hospital Universitario La Paz. CIBERehd, IdiPAZ. Madrid, Spain. [7]Digestive Unit. Hospital Universitario Puerta de Hierro. Majadahonda, Madrid. Spain. CIBERehd. Autonomous University of Madrid. Madrid, Spain

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Correspondence: Antonio Javier Blasco Bravo
e-mail: antoniojblasco@hotmail.com

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ABSTRACT

Background: implementing one-step strategies for hepatitis C diagnosis would help shorten the time to treatment access. Thus avoiding disease progression and complications, while facilitating hepatitis C virus (HCV) elimination.

Objective: to assess the validity and safety of potential one-step strategies for the diagnosis of HCV infection and their associated cost and efficiency.

Methods: the study design is an economic appraisal of efficiency (cost/efficacy) using decision trees and deterministic sensitivity analysis. The analysis was performed from the payer perspective (Spanish National Health System), which exclusively considers the direct costs. Only the differential costs (diagnostic testing costs) were taken into account and the study was set in Spain. The efficacy of a diagnostic strategy was defined as the percentage of patients with an active HCV infection who received a positive diagnosis and the efficiency was defined as the cost per patient with a correctly diagnosed and active infection.

Results: the one-step strategies evaluated for the diagnosis of HCV had an acceptable validity and safety due to the high sensitivity and specificity of the considered tests. The Ab-Ag strategy was the most efficient, followed by Ab-Ag-VL and Ab-VL. Ab-Ag was the most efficient due to the lower cost per patient tested, although the efficacy was lower than the Ab-VL efficacy.

Conclusion: the study findings may help to establish more appropriate one-step diagnostic approaches whilst considering the efficacy and efficiency.

Key words: Chronic hepatitis C. Economic evaluation. Diagnosis.

INTRODUCTION

Hepatitis C is the most common chronic liver condition worldwide. Between 55% and 85% of cases with a hepatitis C virus (HCV) infection progress to a chronic stage and

15-30% will develop cirrhosis and the associated complications in later decades (1,2). The estimated sero-prevalence in the Spanish general population is 1.1% and the prevalence of viremia oscillates between 0.3% and 0.5% (3-5).

Currently, direct antiviral agents (DAAs) that are highly effective against HCV can cure the majority of treated patients (6-8). This has prompted some governments and international organizations to contemplate disease eradication as a goal for 2030 (9-13). The Spanish Ministry of Health, Social Services and Equality published the *Plan Estratégico para el Abordaje de la Hepatitis C* (PEAHC) within the *National Health System* (SNS) in Spain, in May 2015 (14). By virtue of the PEAHC, patients could be treated with the dual aim of curing the disease and avoiding transmission.

Determining the correct diagnosis at the right time is key for infection control (15). However, many patients remain unrecognized and fewer than half of those with a detectable viral load are aware that they have the condition (3,16). Many diagnosed patients either remain untreated or receive treatment with unnecessary delays due to the gap between diagnosis and clinical assessment. A one-step diagnostic approach, which uses one clinical sample for all the tests required for a positive diagnosis of hepatitis C (17-19), followed by an effective communication of the results is paramount. This will avoid the above-mentioned gap and will also facilitate treatment access for all diagnosed patients. Furthermore, this strategy has proven to be cost-effective in comparison to the usual clinical practice (20,21).

Approaches for the diagnosis of HCV infection are highly variable in Spain. There is a wide variability in the service for measuring viral load, the use of confirmatory testing, the use of one-step diagnosis and the way of communicating results. This variability is likely due to a lack of guidelines detailing the diagnostic process, inadequate continuing education, rapidly evolving knowledge and diagnostic-therapeutic technologies, disparities of professionals involved in the diagnosis and resource variability among hospitals (22). Fortunately, the diagnostic resources available in Spanish hospitals form a solid basis for the potential implementation of a one-step HCV diagnosis. However, a one-step diagnosis occurs less frequently than would be technically possible (22).

The aim of this study was to assess the validity (sensitivity and specificity) and safety (predictive values) of various strategies for the one-step diagnosis of HCV infection. Furthermore, the cost and efficiency were also studied, which are key for the selection of the most appropriate test.

METHODOLOGY

A scientific committee (SC) was formed at the start of the study and was made up of three microbiologists and three hepatologists (the authors of the manuscript except AJB and PLM) with experience in the diagnosis and clinical management of HCV infection. The SC was tasked with establishing the potential one-step diagnostic strategies to be considered and providing evidence with regard to their sensitivity, specificity and cost.

Design

This was an economic evaluation study of efficiency (cost-efficacy) using decision trees and deterministic sensitivity analysis. Decision trees were constructed to estimate the validity, safety, cost, efficacy and efficiency of each of the one-step diagnostic approaches suggested by the SC. The analysis was performed from the payer perspective (SNS). The study population was the general population with a given VHC prevalence in Spain.

Construction and development of decision trees

The SC suggested 19 diagnostic strategies and therefore, 19 decision tree models were built, one for each strategy. Each model had as many random nodes as diagnostic tests that were sequentially performed (antibodies [Ab], core antigen [Ag], confirmatory line immunoassay [LIA], viral load by PCR [VL] and genotype [GT]). Three subject profiles were included in each decision tree as follows: a) without antibodies; b) with antibodies and no active infection; and c) with antibodies and active infection. These models were applied to a hypothetical population of 100,000 inhabitants with different combinations of positive Ab prevalence and proportion of viremia-positive subjects.

Evidence sources and probability assignments and calculations

Diagnostic test sensitivity and specificity data were obtained from the best evidence available (Table 1). For Ab and LIA testing, specification documents were obtained from laboratories and from a 2017 publication that discussed assay characteristics for Ag measurement (23). Due to the low limits of detection that VL tests provide, their sensitivity and specificity in the study population (patients with chronic hepatitis C) were deemed to be 100%. Since several Ab tests were available with small differences in sensitivity and specificity, these parameters were estimated as their mean value. All tests were assumed to be used equally in Spain and thus the average sensitivity and specificity were used.

Cost definition and calculation

Only differential costs were considered, i.e., those not shared by all the strategies under study. Consequently, the costs associated with the laboratory tests performed were also collected (Table 2). All diagnostic strategy costs were estimated by multiplying the number of lab tests performed by their unitary cost. Unitary costs were provided by laboratory representatives to the SC (2017 prices plus VAT).

The mean, minimum and maximum cost were considered, as the various Ab and VL tests have different prices and these may vary according to quantity. Costs were estimated as the mean of the available prices. The cost of GT tests was known for different laboratories (Abbott, Roche, Siemens) and there were differences depending on the autonomous communities (ACs). For each test, the mean cost was estimated as the mean cost within the ACs in which the price was known, the maximum cost was the highest price and the minimum cost was the lowest price. GT cost was estimated as the mean cost of the three available tests.

Validity and safety

The validity of the study strategies was assessed by estimating the sensitivity and specificity. Safety was assessed by calculating the positive predictive value (PPV) and negative predictive value (NPV).

Efficacy and efficiency

The efficacy of a diagnostic approach was defined as the percentage of patients with an active HCV infection who received a positive diagnosis. Hence, the efficacy is the strategy sensitivity. Efficiency was defined in terms of cost-efficacy, as the cost of correctly diagnosing a patient with an active infection, i.e., the cost of identifying a true positive (TP) case. An efficiency value of 1 was assigned to the most efficient diagnostic strategy (lowest cost for detecting a TP case), based on which the remaining relative efficiencies were calculated.

Sensitivity analysis

A deterministic sensitivity analysis was performed to estimate the effect derived from the underlying uncertainty of the diagnostic tests (sensitivity, specificity) and their cost. Thus, three scenarios were built as follows: base case, most favorable and least favorable for each diagnostic strategy. The base case scenario considered the mean cost and the mean sensitivity and specificity of the tests used. The most favorable scenario considered the minimum cost and the upper limits of the 95% confidence intervals (95% CI) of the sensitivity and specificity of the test. Finally, the least favorable scenario considered the maximum cost and the lower limits of the 95% CI of the sensitivity and specificity of the test.

Software

The local circumstances of a given hospital or region may differ from those expressed in the present paper. For instance, the prevalence of hepatitis C, availability of diagnostic methods and local prices may differ and vary over time. Thus, a software tool was developed for users in order to calculate the efficacy and efficiency of their diagnostic tests and the associated costs in a given population (in terms of antibody and viremia prevalence). The tool includes the decision tree models for the 19 strategies studied and is freely available at: https://www.dropbox.com/s/heipdo6t1cywjkt/Diagn%C3%B3stico-Hepatitis_C.exe?dl=0

RESULTS

The results are dependent upon population characteristics such as the prevalence of antibodies and the proportion of viremia among subjects with positive antibodies. The results obtained from a sample with characteristics similar to those of the Spanish population (Ab prevalence = 1% and viremia proportion among subjects with positive Abs = 50%) and a high-prevalence sample (Ab prevalence = 30% and viremia proportion among subjects with positive Abs = 70%) are shown as an example. These data were obtained using the three most efficient strategies without genotyping (Table 2) and the three most efficient strategies with genotyping (Table 3 and Fig. 1). These strategies have the highest efficiency regardless of hepatitis C prevalence in the population (Ab prevalence: 0.5-30% and viremia proportion among subjects with positive Abs: 33-70%).

All the one-step HCV diagnostic strategies assessed had an acceptable validity and safety values due to the high sensitivity and specificity of the tests used. The cost per patient tested increases and cost per patient diagnosed with an active infection decreases as the prevalence of antibodies and viremia rises.

Ab-Ag was the most efficient strategy, followed by Ab-Ag-VL and Ab-VL. Ab-Ag was the most efficient strategy due to the lower cost per patient tested. However, it was less efficacious than Ab-VL and obtained fewer TPs and more false negatives (FNs). Furthermore, in the least favorable scenario, Ab-Ag classified patients as having an infection, when actually many were uninfected subjects (false positives).

DISCUSSION

In the absence of an effective vaccine, the cornerstone of HCV elimination or control is the treatment of all patients with the currently available DAAs, which provide cure rates above 95%. To achieve this, patients must be previously diagnosed and referred to treatment facilities. Some studies have shown a delay between diagnosis with HCV infection and adequate treatment (24-27), especially in vulnerable populations (28) such as drug users (29-31). One-step diagnostic strategies would diminish the waiting time to diagnosis and would therefore contribute to a reduction in the time to

treatment access, thus avoiding progression of the disease and its complications, while facilitating HCV elimination. A pilot study in the healthcare areas of Granada and Santiago showed that a one-step diagnosis and the use of red flags for patient referral to specialist care significantly increased the number of subjects assessed for antiviral therapy (32).

In Spain, one-step diagnosis is less commonly used than would be technically feasible (22). Hence, the Spanish Association for the Study of the Liver (Asociación Española para el Estudio del Hígado - AEEH), the Spanish Society of Digestive Diseases (Sociedad Española de Patología Digestiva - SEPD) and the Spanish Society of Infectious Diseases and Clinical Microbiology (Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica - SEIMC GEHEP) have devised a document that recommends one-step diagnosis for active HCV infection. This aims to increase the implementation within Spanish hospitals (33).

A strength of this study was the fact that a sensitivity analysis was performed to identify the potential likelihood range of the efficacy and efficiency of each strategy studied. This helps to manage the uncertainty underlying sensitivity, specificity and the cost of the tests included in the one-step strategies. The results may vary according to population characteristics in terms of antibody and viremia prevalence. Therefore, a computer application was developed for users to estimate the efficacy and efficiency of each strategy, considering the specific tests involved and their costs. This software is freely available at: https://www.dropbox.com/s/heipdo6t1cywjkt/Diagn%C3%B3stico-Hepatitis_C.exe?dl=0

It seems inappropriate to issue a general recommendation on the use of any specific one-step diagnostic approach since the results are dependent on population characteristics. The computer application developed to facilitate decision making means that users will have all the information required for identifying the most appropriate strategy in their specific setting, according to the criteria they deem most relevant (e.g., efficiency, efficacy or false negatives avoided).

The findings of this study may help to establish the most appropriate strategies in terms of efficacy and efficiency. This fact is relevant as healthcare systems are meant to maximize health outcomes in the population with the available resources, which are

inherently limited. In this context, ensuring health system sustainability requires efficient resource utilization. Economic evaluation studies, as this one, may help healthcare professionals, managers and policy makers to improve decision-making with regard to diagnostic strategies for HCV infection.

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Table 1. Sensitivity, specificity and cost of the diagnostic tests

	Sensitivity			*Specificity*			*Price (euros)*		
Test (laboratory)	*Mean*	*LL-CI*	*UL-CI*	*Mean*	*LL-CI*	*UL-CI*	*Mean*	*Minimum*	*Maximum*
Antibody (Ab)									
Advia Centaur HCV (Siemens)	1.0000	0.9918	1.0000	0.9990	0.9978	0.9997	3.27	3.27	3.27
Liaison XL Murex HCV Ab (DiaSorin)	1.0000	0.9946	1.0000	0.9970	0.9951	0.9983	3.03	3.03	3.03
Architect Anti-HCV (Abbott)	0.9910	0.9677	0.9989	0.9960	0.9945	0.9971	3.93	3.03	4.84
Elecsys Anti-HCV II (Roche)	1.0000	0.9961	1.0000	0.9984	0.9971	0.9992	2.69	2.66	2.72
Access HCV Ab V3 (Beckman Coulter)	1.0000	0.9930	1.0000	0.9986	0.9972	0.9995	3.78	3.78	3.78
Estimated	0.9982	0.9886	0.9998	0.9978	0.9963	0.9988	3.34	3.15	3.53
Core antigen (Ag)									
Architect HCV Ag Assay (Abbott)	0.9910	0.9680	0.9990	1.0000	0.9470	1.0000	16.34	14.52	18.15
Confirmatory line immunoassay (LIA)									
Bioblot HCV	1.0000	0.9448	1.0000	1.0000	0.9538	1.0000	39.20	39.20	39.20
Viral load (VL)									
Artus HCV QS-RGQ kit (Qiagen)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	30.25	24.20	36.30
Abbott RealTime HCV (Abbott)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	39.33	36.30	42.35
Aptima HCV Quant Dx assay (Hologic)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	36.30	36.30	36.30

Cobas AP/Cobas TaqMan HCV Quantitative Test v2,0 (ROCHE)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	48.40	48.40	48.40
VERSANT HCV RNA 1.0 Assay (kPCR) (Siemens)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	39.33	36.30	42.35
Estimated	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	38.72	36.30	41.14
VL point of care									
Xpert HCV Viral Load (CEPHEID)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	54.45	54.45	54.45
Genotype (estimated)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	57.24	45.59	68.03

LL-CI: lower limit of the 95% confidence intervals; UL-CI: upper limit of the 95% confidence intervals.

Table 2. **Validity, safety, cost and efficiency of the three most efficient strategies without genotyping (population of 100,000 inhabitants)**

Strategy	*TP*	*FN*	*TN*	*FP*	*Validity*		*Safety*		*Cost*	*Efficiency*	
					Sensitivity	*Specificity*	*PPV*	*NPV*	*Cost (€)**	*Cost/TP (€)*[†]	*Relative*
Population: Ab = 1%; viremia = 50%											
Base case scenario											
Ab-VL	499.10	0.90	99,500.00	0.00	0.99820	1.00000	1.00000	0.99999	3.809	763.22	1.067
Ab-Ag	494.61	5.39	99,500.00	0.00	0.98922	1.00000	1.00000	0.99995	3.537	715.12	1.000
Ab-Ag-VL	494.61	5.39	99,500.00	0.00	0.98922	1.00000	1.00000	0.99995	3.729	753.84	1.054
Most favorable scenario											
Ab-VL	499.89	0.11	99,500.00	0.00	0.99978	1.00000	1.00000	1.00000	3.558	711.82	1.073
Ab-Ag	499.39	0.61	99,500.00	0.00	0.99878	1.00000	1.00000	0.99999	3.314	663.58	1.000
Ab-Ag-VL	499.39	0.61	99,500.00	0.00	0.99878	1.00000	1.00000	0.99999	3.495	699.88	1.055

Least favorable scenario											
Ab-VL	494.32	5.68	99,500.00	0.00	0.98864	1.00000	1.00000	0.99994	4.082	825.73	1.048
Ab-Ag	478.50	21.50	99,454.60	45.40	0.95700	0.99954	0.91334	0.99978	3.771	788.11	1.000
Ab-Ag-VL	478.50	21.50	99,500.00	0.00	0.95700	1.00000	1.00000	0.99978	3.987	833.16	1.057
Population: Ab = 30%; viremia = 70%											
Base case scenario											
Ab-VL	20,962.20	37.80	79,000.00	0.00	0.99820	1.00000	1.00000	0.99952	14.993	71.52	1.800
Ab-Ag	20,773.54	226.46	79,000.00	0.00	0.98922	1.00000	1.00000	0.99714	8.255	39.74	1.000
Ab-Ag-VL	20,773.54	226.46	79,000.00	0.00	0.98922	1.00000	1.00000	0.99714	16.299	78.46	1.974
Most favorable scenario											
Ab-VL	20,995.38	4.62	79,000.00	0.00	0.99978	1.00000	1.00000	0.99994	14.070	67.01	1.870

Ab-Ag	20,974.38	25.62	79,000.00	0.00	0.99878	1.00000	1.00000	0.99968	7.518	35.85	1.000
Ab-Ag-VL	20,974.38	25.62	79,000.00	0.00	0.99878	1.00000	1.00000	0.99968	15.132	72.15	2.013
Least favorable scenario											
Ab-VL	20,761.44	238.56	79,000.00	0.00	0.98864	1.00000	1.00000	0.99699	15.833	76.26	1.711
Ab-Ag	20,097.07	902.93	78,514.84	485.16	0.95700	0.99386	0.97643	0.98863	8.956	44.56	1.000
Ab-Ag-VL	20,097.07	902.93	79,000.00	0.00	0.95700	1.00000	1.00000	0.98870	17.423	86.69	1.946

TP: true positive; FN: false negative; TN: true negative; FP: false positive; PPV: positive predictive value; NPV: negative predictive value; Ab: antibody testing; Ag: core antigen testing; VL: viral load by PCR. *Cost per patient tested. †Cost per patient diagnosed with active infection.

Table 3. **Validity, safety, cost and efficiency of the three most efficient strategies with genotyping (population of 100,000 inhabitants)**

					Validity		*Safety*		*Cost*	*Efficiency*	
Strategy	*TP*	*FN*	*TN*	*FP*	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*Cost (€)**	*Cost/TP (€)*[†]	*Relative*
Population: Ab = 1%; viremia = 50%											
Base case scenario											
Ab-VL-GT	499.10	0.90	99,500.00	0.00	0.99820	1.00000	1.00000	0.99999	4.095	820.46	1.062
Ab-Ag-GT	494.61	5.39	99,500.00	0.00	0.98922	1.00000	1.00000	0.99995	3.820	772.36	1.000
Ab-Ag-VL-GT	494.61	5.39	99,500.00	0.00	0.98922	1.00000	1.00000	0.99995	4.012	811.08	1.050
Most favorable scenario											
Ab-VL-GT	499.89	0.11	99,500.00	0.00	0.99978	1.00000	1.00000	1.00000	3.786	757.41	1.068
Ab-Ag-GT	499.39	0.61	99,500.00	0.00	0.99878	1.00000	1.00000	0.99999	3.541	709.16	1.000
Ab-Ag-VL-GT	499.39	0.61	99,500.00	0.00	0.99878	1.00000	1.00000	0.99999	3.723	745.46	1.051

Least favorable scenario											
Ab-VL-GT	494.32	5.68	99,500.00	0.00	0.98864	1.00000	1.00000	0.99994	4.418	893.75	1.036
Ab-Ag-GT	478.50	21.50	99,500.00	0.00	0.95700	1.00000	1.00000	0.99978	4.128	862.60	1.000
Ab-Ag-VL-GT	478.50	21.50	99,500.00	0.00	0.95700	1.00000	1.00000	0.99978	4.312	901.18	1.045
Population: Ab = 30%; viremia = 70%											
Base case scenario											
Ab-VL-GT	20,962.20	37.80	79,000.00	0.00	0.99820	1.00000	1.00000	0.99952	26.992	128.77	1.328
Ab-Ag-GT	20,773.54	226.46	79,000.00	0.00	0.98922	1.00000	1.00000	0.99714	20.146	96.98	1.000
Ab-Ag-VL-GT	20,773.54	226.46	79,000.00	0.00	0.98922	1.00000	1.00000	0.99714	28.190	135.70	1.399
Most favorable scenario											
Ab-VL-GT	20,995.38	4.62	79,000.00	0.00	0.99978	1.00000	1.00000	0.99994	23.641	112.60	1.383

Ab-Ag-GT	20,974.38	25.62	79,000.00	0.00	0.99878	1.00000	1.00000	0.99968	17.080	81.43	1.000
Ab-Ag-VL-GT	20,974.38	25.62	79,000.00	0.00	0.99878	1.00000	1.00000	0.99968	24.694	117.73	1.446
Least favorable scenario											
Ab-VL-GT	20,761.44	238.56	79,000.00	0.00	0.98864	1.00000	1.00000	0.99699	29.956	144.29	1.263
Ab-Ag-GT	20,097.07	902.93	79,000.00	0.00	0.95700	1.00000	1.00000	0.98870	22.957	114.23	1.000
Ab-Ag-VL-GT	20,097.07	902.93	79,000.00	0.00	0.95700	1.00000	1.00000	0.98870	31.094	154.72	1.354

TP: true positive; FN: false negative; TN: true negative; FP: false positive; PPV: positive predictive value; NPV: negative predictive value; Ab: antibody testing; Ag: core antigen testing; VL: viral load by PCR; GT: genotype testing. *Cost per patient tested. †Cost per patient diagnosed with active infection.

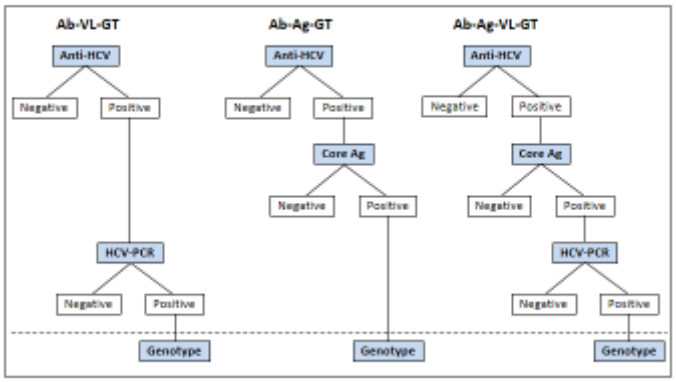

Fig. 1. Decision tree models of the most efficient strategies with and without genotyping. Ab, anti-HCV: antibody testing; Ag, core Ag: core antigen testing; VL, HCV-PCR: HCV viral load by PCR; GT, genotype: genotype testing (absent in non-genotyping strategies).