Anexa nr. 7
la Documentația standard nr._____
din "____" _____ 20___

CERERE DE PARTICIPARE

Către **CENTRUL PENTRU ACHIZITII PUBLICE CENTRALIZATE IN SĂNĂTATE**

Stimaţi domni,

Ca urmare a anunțului/invitației de participare/de preselecție apărut în Buletinul achizițiilor publice și/sau Jurnalul Oficial al Uniunii Europene, nr ocds-b3wdp1-MD-1720528223328 ***Privind încheierea acordului-cadru - Achiziționarea dispozitivelor medicale conform Programului Naţional de combaterea hepatitelor virale B, C și D pentru anii 2025-2027***, noi Medist Grup SRL, am luat cunoștință de condițiile și de cerințele expuse în documentația de atribuire și exprimăm prin prezenta interesul de a participa, în calitate de ofertant/candidat, neavînd obiecții la documentația de atribuire.

Data completării 15.08.2024

Digitally signed by Anghel Gabriela-Cristina
Date: 2024.08.15 13:20:51 EEST
Reason: MoldSign Signature
Location: Moldova
MOLDOVA EUROPEANĂ

Cu stimă,
Ofertant/candidat
Gabriela-Cristina Anghel

MEDIST Grup S.R.L.
Str. Mitropolit Gavriil Bănulescu-Bodoni nr. 25
Oficiul 33, MD-2012 Chișinău, Rep. Moldova
Tel./Fax: +373 22 84 94 95
E-mail: office@medist.md
Web: www.medist.md

IDNO: 1018600004516
TVA: 0508191
BC Victoriabank SA, Filiala nr. 26 Chișinău
IBAN (MDL):MD57VI022242600000269MDL
SWIFT: VICBMD2X469

ORDIN DE PLATA NR.388 Tip.doc. 1

DATA EMITERII: 14 august 2024

PLATITI:129211-70 LEI: Una Suta Douazeci si Noua Mii Doua Sute Unsprezece, 70

PLATITOR: (R)MEDIST GRUP SRL CODUL IBAN:MD57VI022242600000269MDL
CODUL FISCAL:1018600004516

PRESTATORUL PLATITOR
B.C VictoriaBank S.A. s.26 Chisinau

BENEFICIAR:(R) CENTRUL PENTRU ACHIZITII P UBLICE CENTRALIZATE IN SANATATE CODUL IBAN:MD23TRPCCC518430B01859AA
CODUL FISCAL:1016601000212

PRESTATORUL BENEFICIAR
Min.Finantelor-Trezoreria de Stat

DESTINATIA PLATII: /P102/129211,70 Garantia pentru oferta in valoare de 2 procente, pentru procedura de achizitie publica nr. 21252006 din 09.07.2024. Fara TVA.

NORMAL/URGENT:NO

L.S.

CODUL TRANZACTIEI:101

DATA PRIMIRII: _____

DATA EXECUTARII: _____

SEMNATURILE EMITENTULUI

_____
SEMNATURA PRESTATORULUI

«VICTORIABANK»
DIRECȚIA OPERAȚIUNI
14. AUG. 2024
Cod fiscal 1002600001338 SWIFT VICBMD2X
Cod IBAN MD81VI0000000000235216701

MOTIVUL REFUZULUI L.S.

15:32:06 14 AUG 2024
Semnatura electronica:
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eWMebSZ4YLpDKjpE17cXkfncNzG4gTJeKaJ8BxHKjgptD+Oq6BNhKOwV/t39Ls64ppK7ihlYtDNv
u2l/gE5ZJOMsTW20YesU7yHbAo+G9R5aFdCKFA==

I.P. "AGENȚIA SERVICII PUBLICE"
Departamentul înregistrare și licențiere a unităților de drept

Extras
din Registrul de stat al persoanelor juridice
nr. **117493** din **15.09.2023**

Denumirea completă: **Societatea cu Răspundere Limitată "MEDIST GRUP"**
Denumirea prescurtată: **"MEDIST GRUP" S.R.L.**
Forma juridică de organizare: **Societate cu răspundere limitată**
Numărul de identificare de stat și codul fiscal: **1018600004516**
Data înregistrării de stat: **02.02.2018**
Sediu: **MD-2012, strada Mitropolit Gavriil Bănulescu-Bodoni 25, ap. 33, mun. Chişinău, Republica Moldova**
Genurile de activitate:

1. **Comerţ cu ridicata al produselor farmaceutice;**
2. **Comerţ cu ridicata nespecializat;**
3. **Repararea echipamentelor electronice şi optice;**
4. **Activităţi de testare şi analize tehnice;**
5. **Comerţ cu amănuntul al articolelor medicale şi ortopedice, în magazine specializate;**

Capitalul social: **373026 Lei**
Administrator: **ANGHEL GABRIELA-CRISTINA IDNP 2017803985939**
Asociați:

1. **MEDIST IMAGING & P.O.C. S.R.L., partea socială 6244 Euro, ce constituie 33.00%**
2. **MEDIST LIFE SCIENCE S.R.L., partea socială 6244 Euro, ce constituie 33.00%**
3. **MEDIST S.R.L., partea socială 6433 Euro, ce constituie 34.00%**

Beneficiari efectivi: **MANOLE IONEL, KLUMPNER CATALINA ANA, VLĂDESCU CARMEN, VLĂDESCU SEBASTIAN-ALEXANDRU**

Prezentul extras este eliberat în temeiul art. 34 al Legii nr.220/2007 privind înregistrarea de stat a persoanelor juridice şi a întreprinzătorilor individuali şi confirmă datele din Registrul de stat la data de 15.09.2023

Specialist coordonator
Marina Franţuz
tel. 022-207837

GUVERNUL REPUBLICII MOLDOVA

SERVICIUL FISCAL DE STAT

MCabinet
PORTALUL GUVERNAMENTAL AL CETĂȚEANULUI ȘI AL UNITĂȚILOR DE DREPT

CERTIFICAT

privind lipsa sau existența restanțelor față de bugetul public național

Nr. № **0834516**

Din От **15.08.2024 08:34**

DATE DESPRE CONTRIBUABIL / ИНФОРМАЦИЯ О НАЛОГОПЛАТЕЛЬЩИКЕ

Codul fiscal / Numărul de identificare
Фискальный код / Идентификационный номер

1018600004516

Denumirea
Наименование

Societatea cu Răspundere Limitată MEDIST GRUP

ATESTAREA LIPSEI SAU EXISTENȚEI RESTANȚELOR CONFORM DATELOR SISTEMULUI INFORMAȚIONAL AUTOMATIZAT / ПОДТВЕРЖДЕНИЕ ОТСУТСВИЯ ИЛИ НАЛИЧИЯ ЗАДОЛЖНОСТЕЙ СОГЛАСНО ДАННЫМ ИНФОРМАЦИОННОЙ АВТОМАТИЗИРОВАННОЙ СИСТЕМЫ

La data emiterii prezentului certificat restanța față de bugetul public național constituie
На дату выдачи данной справки задолжность перед национальном публичным бюджетом составляет

0 MDL

VALABIL PÂNĂ LA / ДЕЙСТВИТЕЛЕН ДО **30.08.2024 08:34**

Prezentul document este eliberat în temeiul Art. 29, alin. (3) din Legea cu privire la registre nr. 71/2007 și în baza datelor furnizate de Serviciul Fiscal de Stat în Portalul Guvernamental al Cetățeanului și al Unităților de Drept / Справка выдана в соответсвие со ст. 29 п. (3) Закона о реестрах № 71/2007 на основании данных, предостоставленных Государственной налоговой службой на Портале Правительства Гражданина и Юридических Лиц.

Generat și semnat de Portalul Guvernamental al Cetățeanului și al Unităților de Drept la **15.08.2024 08:34**

Prezentul certificat este semnat electronic în conformitate cu Legea nr.124 din 19.05.2022
Сертификат подписан электронной попдписью в соответсвие с Законом № 124 от 19.05.2022

Certificatul este descărcat din Portalul Guvernamental al Cetățeanului și al Unităților de Drept (mcabinet.gov.md) și este semnat electronic de către posesorul acestui portal și are aceiași valoare juridică ca și documentele eliberate pe suport de hârtie de către organele cu atribuții de administrare fiscală. Verificarea autenticității semnăturii electronice poate fi realizată cu ajutorul Serviciului Guvernamental de Semnătură Electronică (msign.gov.md)

Сертификат скачен с Правительственного Портала Гражданина и Юридических Лиц (mcabinet.gov.md) и подписан электронной подписью владельца портала и имеет такаю же юридическую силу, как и документы выдаваемые на бумаге органами налоговой администрации. Проверку подлиности электронной подписи можно осуществить с помощью Государсвенной Службой Электронной Подписью (msign.gov.md)

VICTORIABANK
PRIMA BANCĂ DIN MOLDOVA

www.victoriabank.md

Filiala nr. 26 Chișinău
str. Mt. Bănulescu-Bodoni, 28/1
MD-2005, mun. Chișinău
Tel.: (+373 22) 92-92-52
Fax: (+373 22) 78-47-30
SWIFT: VICBMD2X469
IDNO 1002600001338
Capital social – 250 000 910 lei
www.victoriabank.md

Nr. 26/466 din "19" iunie 2018

La Nr. 395 din "19" iunie 2018

Secret bancar
Confidențial

CERTIFICAT

Prin prezentul, BC "VICTORIABANK" SA Sucursala nr.26 Chişinău, codul băncii VICBMD2X469, cod fiscal 1002600001338, confirmă că MEDIST GRUP SRL, cod fiscal 1018600004516, deţine următoarele conturi curente în format IBAN:

MD57VI022242600000269MDL;
MD76VI022242600000105USD;
MD61VI022242600000116EUR;
MD83VI022242600000008RON.

Certificatul este eliberat la cererea clientului pentru a fi prezentat la destinaţie.

Cebanu Valentina
Director

REPUBLICA MOLDOVA, mun. CHIŞINĂU * BANCA COMERCIALĂ "VICTORIABANK" S.A. * SUCURSALA Nr.26 CHIŞINĂU Nr. 1002600001338

Blanovscaia Anna
Contabil-şef

Ex: Scutaru Lilia
tel. 022 78-47-32

Anexe la SNC
"Prezentarea situatiilor financiare"
Aprobat de Ministerul Finantelor
al Republicii Moldova

SITUAŢIILE FINANCIARE

pentru perioada 01.01.2023 - 31.12.2023

Entitatea: MEDIST GRUP S.R.L.
Cod CUIÎO: 41247072
Cod IDNO: 1018600004516

Sediul:
MD:
Raionul(municipiul): 105, DDF BUIUCANI
Cod CUATM: 0120, SEC.BUIUCANI
Strada: Mitropolit Gavriil Banulescu-Bodoni nr.25 of.33

Activitatea principală: G4646, Comert cu ridicata al produselor farmaceutice
Forma de proprietate: 23, Proprietatea statelor străine
Forma organizatorico-juridică: 530, Societăți cu răspundere limitată

Date de contact:
Telefon: 06868147
WEB:
E-mail: natalia.mutu@medist.md
Numele și coordonatele al contabilului-șef: Dl (dna) Natalia Mutu Tel. 068681147

Numărul mediu al salariaților în perioada de gestiune: 5 **persoane.**

Persoanele responsabile de semnarea situațiilor financiare* Gabriela Anghel-Cristina

Unitatea de măsură: leu

BILANŢUL

Anexa 1

la 31.12.2023

Nr. cpt.	Indicatori	Cod rd.	Sold la	
			Începutul perioadei de gestiune	Sfîrșitul perioadei de gestiune
1	2	3	4	5
	A C T I V			
A.	**ACTIVE IMOBILIZATE** **I. Imobilizări necorporale**			
	1. Imobilizări necorporale în curs de execuție	010		
	2. Imobilizări necorporale în exploatare, total	020		
	din care: 2.1. concesiuni, licențe și mărci	021		
	2.2. drepturi de autor și titluri de protecție	022		
	2.3. programe informatice	023		
	2.4. alte imobilizări necorporale	024		

3. Fond comercial	030		
4. Avansuri acordate pentru imobilizări necorporale	040		
Total imobilizări necorporale (rd.010 + rd.020 + rd.030 + rd.040)	050		
II. Imobilizări corporale			
1. Imobilizări corporale în curs de execuție	060		
2. Terenuri	070		
3. Mijloace fixe, total	080	3028298	3859991
din care: 3.1. clădiri	081		
3.2. construcții speciale	082		
3.3. mașini, utilaje și instalații tehnice	083	3018214	3854288
3.4. mijloace de transport	084		
3.5. inventar și mobilier	085		
3.6. alte mijloace fixe	086	10084	5703
4. Resurse minerale	090		
5. Active biologice imobilizate	100		
6. Investiții imobiliare	110		
7. Avansuri acordate pentru imobilizări corporale	120	141992	141992
Total imobilizări corporale (rd.060 + rd.070 + rd.080 + rd.090 + rd.100 + rd.110 + rd.120)	130	3170290	4001983
III. Investiții financiare pe termen lung			
1. Investiții financiare pe termen lung în părți neafiliate	140		
2. Investiții financiare pe termen lung în părți afiliate, total	150		
din care: 2.1. acțiuni și cote de participație deținute în părțile afiliate	151		
2.2 împrumuturi acordate părților afiliate	152		
2.3 împrumuturi acordate aferente intereselor de participare	153		
2.4 alte investiții financiare	154		
Total investiții financiare pe termen lung (rd.140 + rd.150)	160		
IV. Creanțe pe termen lung și alte active imobilizate			
1. Creanțe comerciale pe termen lung	170		
2. Creanțe ale părților afiliate pe termen lung	180		
inclusiv: creanțe aferente intereselor de participare	181		
3. Alte creanțe pe termen lung	190		
4. Cheltuieli anticipate pe termen lung	200		

	5. Alte active imobilizate	210		
	Total creanțe pe termen lung și alte active imobilizate (rd.170 + rd.180 + rd.190 + rd.200 + rd.210)	220		
	TOTAL ACTIVE IMOBILIZATE (rd.050 + rd.130 + rd.160 + rd.220)	230	3170290	4001983
B.	**ACTIVE CIRCULANTE** **I. Stocuri**			
	1. Materiale și obiecte de mică valoare și scurtă durată	240	31649	63405
	2. Active biologice circulante	250		
	3. Producția în curs de execuție	260		
	4. Produse și mărfuri	270	852838	765931
	5. Avansuri acordate pentru stocuri	280		
	Total stocuri (rd.240 + rd.250 + rd.260 + rd.270 + rd.280)	290	884487	829336
	II. Creanțe curente și alte active circulante			
	1. Creanțe comerciale curente	300	3969789	2559140
	2. Creanțe ale părților afiliate curente	310		
	inclusiv: creanțe aferente intereselor de participare	311		
	3. Creanțe ale bugetului	320	982652	991266
	4. Creanțele ale personalului	330	856	300
	5. Alte creanțe curente	340	1093188	1838152
	6. Cheltuieli anticipate curente	350	48056	10942
	7. Alte active circulante	360		27708
	Total creanțe curente și alte active circulante (rd.300 + rd.310 + rd.320 + rd.330 + rd.340 + rd.350 + rd.360)	370	6094541	5427508
	III. Investiții financiare curente			
	1. Investiții financiare curente în părți neafiliate	380		
	2. Investiții financiare curente în părți afiliate, total	390		
	din care: 2.1. acțiuni și cote de participație deținute în părțile afiliate	391		
	2.2. împrumuturi acordate părților afiliate	392		
	2.3. împrumuturi acordate aferente intereselor de participare	393		
	2.4. alte investiții financiare în părți afiliate	394		
	Total investiții financiare curente (rd.380 + rd.390)	400		
	IV. Numerar și documente bănești	410	4161583	3229017
	TOTAL ACTIVE CIRCULANTE (rd.290 + rd.370 + rd.400 + rd.410)	420	11140611	9485861
	TOTAL ACTIVE	430	14310901	13487844

	(rd.230 + rd.420)			
	P A S I V			
C.	**CAPITAL PROPRIU** **I. Capital social și neînregistrat**			
	1. Capital social	440	373026	373026
	2. Capital nevărsat	450	( )	( )
	3. Capital neînregistrat	460		
	4. Capital retras	470	( )	( )
	5. Patrimoniul primit de la stat cu drept de proprietate	480		
	Total capital social și neînregistrat (rd.440 + rd.450 + rd.460 + rd.470 + rd.480)	490	373026	373026
	II. Prime de capital	500		
	III. Rezerve			
	1. Capital de rezervă	510		
	2. Rezerve statutare	520		
	3. Alte rezerve	530		
	Total rezerve (rd.510 + rd.520 + rd.530)	540		
	IV. Profit (pierdere)			
	1. Corecții ale rezultatelor anilor precedenți	550	X	-103
	2. Profit nerepartizat (pierdere neacoperită) al anilor precedenți	560	5402413	5402413
	3. Profit net (pierdere netă) al perioadei de gestiune	570	X	318340
	4. Profit utilizat al perioadei de gestiune	580	X	( )
	Total profit (pierdere) (rd.550 + rd.560 + rd.570 + rd.580)	590	5402413	5720650
	V. Rezerve din reevaluare	600		
	VI. Alte elemente de capital propriu	610		
	TOTAL CAPITAL PROPRIU (rd.490 + rd.500 + rd.540 + rd.590 + rd.600 + rd.610)	620	5775439	6093676
D.	**DATORII PE TERMEN LUNG**			
	1. Credite bancare pe termen lung	630		
	2. Împrumuturi pe termen lung	640	1579325	1307469
	din care: 2.1. împrumuturi din emisiunea de obligațiuni	641		
	inclusiv: împrumuturi din emisiunea de obligațiuni convertibile	642		
	2.2. alte împrumuturi pe termen lung	643	1579325	1307469
	3. Datorii comerciale pe termen lung	650		299803

	4. Datorii față de părțile afiliate pe termen lung	660		
	inclusiv: datorii aferente intereselor de participare	661		
	5. Avansuri primite pe termen lung	670		
	6. Venituri anticipate pe termen lung	680		
	7. Alte datorii pe termen lung	690		
	TOTAL DATORII PE TERMEN LUNG (rd.630 + rd.640 + rd.650 + rd.660 + rd.670 + rd.680 + rd.690)	700	1579325	1607272
E.	**DATORII CURENTE**			
	1. Credite bancare pe termen scurt	710		
	2. Împrumuturi pe termen scurt, total	720	1344767	951672
	din care: 2.1. împrumuturi din emisiunea de obligațiuni	721		
	inclusiv: împrumuturi din emisiunea de obligațiuni convertibile	722		
	2.2. alte împrumuturi pe termen scurt	723	1344767	951672
	3. Datorii comerciale curente	730	2165195	100772
	4. Datorii față de părțile afiliate curente	740	3446175	4692920
	inclusiv: datorii aferente intereselor de participare	741		
	5. Avansuri primite curente	750		
	6. Datorii față de personal	760		
	7. Datorii privind asigurările sociale și medicale	770		28990
	8. Datorii față de buget	780		12542
	9. Datorii față de proprietari	790		
	10. Venituri anticipate curente	800		
	11. Alte datorii curente	810		
	TOTAL DATORII CURENTE (rd.710 + rd.720 + rd.730 + rd.740 + rd.750 + rd.760 + rd.770 + rd.780 + rd.790 + rd.800 + rd.810)	820	6956137	5786896
F.	**PROVIZIOANE**			
	1. Provizioane pentru beneficiile angajaților	830		
	2. Provizioane pentru garanții acordate cumpărătorilor/clienților	840		
	3. Provizioane pentru impozite	850		
	4. Alte provizioane	860		
	TOTAL PROVIZIOANE (rd.830 + rd.840 + rd.850 + rd.860)	870		
	TOTAL PASIVE (rd.620 + rd.700 + rd.820 + rd.870)	880	14310901	13487844

SITUAŢIA DE PROFIT ŞI PIERDERE

de la 01.01.2023 pînă la 31.12.2023

Anexa 2

Indicatori	Cod rd.	Perioada de gestiune

		precedenta	curenta
1	2	3	4
Venituri din vînzări, total	010	29021092	20271056
din care: venituri din vînzarea produselor și mărfurilor	011	28497093	19719964
venituri din prestarea serviciilor și executarea lucrărilor	012	126338	211868
venituri din contracte de construcție	013		
venituri din contracte de leasing	014		
venituri din contracte de microfinanţare	015		
alte venituri din vînzări	016	397661	339224
Costul vînzărilor, total	020	20867803	15060163
din care: valoarea contabilă a produselor și mărfurilor vîndute	021	20867803	15060163
costul serviciilor prestate și lucrărilor executate terților	022		
costuri aferente contractelor de construcție	023		
costuri aferente contractelor de leasing	024		
costuri aferente contractelor de microfinanţare	025		
alte costuri aferente vînzărilor	026		
Profit brut (pierdere brută) (rd.010 - rd.020)	030	8153289	5210893
Alte venituri din activitatea operațională	040	135089	66300
Cheltuieli de distribuire	050	118118	146520
Cheltuieli administrative	060	4920088	4367490
Alte cheltuieli din activitatea operațională	070	1931079	570712
Rezultatul din activitatea operațională: profit (pierdere) (rd.030 + rd.040 - rd.050 - rd.060 - rd.070)	080	1319093	192471
Venituri financiare, total	090	786797	991278
din care: venituri din interese de participare	091		
inclusiv: veniturile obținute de la părțile afiliate	092		
venituri din dobînzi	093		
inclusiv: veniturile obținute de la părțile afiliate	094		
venituri din alte investiții financiare pe termen lung	095		
inclusiv: veniturile obținute de la părțile afiliate	096		
venituri aferente ajustărilor de valoare privind investițiile financiare pe termen lung și curente	097		
venituri din ieșirea investițiilor financiare	098		
venituri aferente diferențelor de curs valutar și de sumă	099	786797	991278

Cheltuieli financiare, total	100	904528	804089
din care: cheltuieli privind dobînzile	101		
inclusiv: cheltuielile aferente părților afiliate	102		
cheltuieli aferente ajustărilor de valoare privind investițiile financiare pe termen lung și curente	103		
cheltuieli aferente ieșirii investițiilor financiare	104		
cheltuieli aferente diferențelor de curs valutar și de sumă	105	904528	804089
Rezultatul: profit (pierdere) financiar(ă) (rd.090 - rd.100)	110	-117731	187189
Venituri cu active imobilizate și excepționale	120	5290	281416
Cheltuieli cu active imobilizate și excepționale	130		200390
Rezultatul din operațiuni cu active imobilizate și excepționale: profit (pierdere) (rd.120 - rd.130)	140	5290	81026
Rezultatul din alte activități: profit (pierdere) (rd.110 + rd.140)	150	-112441	268215
Profit (pierdere) pînă la impozitare (rd.080 + rd.150)	160	1206652	460686
Cheltuieli privind impozitul pe venit	170	380423	142346
Profit net (pierdere netă) al perioadei de gestiune (rd.160 - rd.170)	180	826229	318340

SITUAŢIA MODIFICĂRILOR CAPITALULUI PROPRIU

de la 01.01.2023 pînă la 31.12.2023

Anexa 3

Nr. d/o	Indicatori	Cod rd	Sold la începutul perioadei de gestiune	Majorări	Diminuări	Sold la sfîrșitul perioadei de gestiune
1	2	3	4	5	6	7
I.	**Capital social și neînregistrat**					
	1. Capital social	010	373026			373026
	2. Capital nevărsat	020	( )	( )	( )	( )
	3. Capital neînregistrat	030				
	4. Capital retras	040	( )	( )	( )	( )
	5. Patrimoniul primit de la stat cu drept de proprietate	050				
	Total capital social și neînregistrat (rd.010 + rd.020 + rd.030 + rd.040 + rd.050)	060	373026			373026
II.	**Prime de capital**	070				
III.	**Rezerve**					
	1. Capital de rezervă	080				
	2. Rezerve statutare	090				

	3. Alte rezerve	100				
	Total rezerve (rd.080 + rd.090 + rd.100)	110				
IV.	**Profit (pierdere)**					
	1. Corecții ale rezultatelor anilor precedenți	120	X		103	-103
	2. Profit nerepartizat (pierdere neacoperită) al anilor precedenți	130	5402413	826229	826229	5402413
	3. Profit net (pierdere netă) al perioadei de gestiune	140	X	318340		318340
	4. Profit utilizat al perioadei de gestiune	150	X	( )	( )	( )
	Total profit (pierdere) (rd.120 + rd.130 + rd.140 + rd.150)	160	5402413	1144569	826332	5720650
V.	**Rezerve din reevaluare**	170				
VI.	**Alte elemente de capital propriu**	180				
	Total capital propriu (rd.060 + rd.070 + rd.110 + rd.160 + rd.170 + rd.180)	190	5775439	1144569	826332	6093676

SITUAŢIA FLUXURILOR DE NUMERAR

de la 01.01.2023 pînă la 31.12.2023

Anexa 4

Indicatori	Cod rd	Perioada de gestiune	
		precedentă	curentă
1	2	3	4
Fluxuri de numerar din activitatea operațională			
Încasări din vînzări	010	29053578	24793777
Plăți pentru stocuri și servicii procurate	020	20406745	19703580
Plăți către angajați și organe de asigurare socială și medicală	030	2732087	1905611
Dobînzi plătite	040		19210
Plata impozitului pe venit	050	1868681	169911
Alte încasări	060	5290	
Alte plăți	070	1588647	3499117
Fluxul net de numerar din activitatea operațională (rd.010 - rd.020 - rd.030 - rd.040 - rd.050 + rd.060 - rd.070)	080	2462708	-503652
Fluxuri de numerar din activitatea de investiții			
Încasări din vînzarea activelor imobilizate	090		
Plăți aferente intrărilor de active imobilizate	100		
Dobînzi încasate	110		
Dividende încasate	120		
inclusiv: dividende încasate din străinătate	121		

Alte încasări (plăți)	130		
Fluxul net de numerar din activitatea de investiții (rd.090 - rd.100 + rd.110 + rd.120 ± rd.130)	140		
Fluxuri de numerar din activitatea financiară			
Încasări sub formă de credite și împrumuturi	150		800000
Plăți aferente rambursării creditelor și împrumuturilor	160	1457991	1375308
Dividende plătite	170		
inclusiv: dividende plătite nerezidenților	171		
Încasări din operațiuni de capital	180		
Alte încasări (plăți)	190		
Fluxul net de numerar din activitatea financiară (rd.150 - rd.160 - rd.170 + rd.180 ± rd.190)	200	-1457991	-575308
Fluxul net de numerar total (± rd.080 ± rd.140 ± rd.200)	210	1004717	-1078960
Diferențe de curs valutar favorabile (nefavorabile)	220	73028	146394
Sold de numerar la începutul perioadei de gestiune	230	3083838	4161583
Sold de numerar la sfîrşitul perioadei de gestiune (± rd.210 ± rd.220 + rd.230)	240	4161583	3229017

Documente atașate - Notă explicativă (fișierul pdf)

Recipisa 2

Respondent
Codul fiscal: 1018600004516, denumire: MEDIST GRUP S.R.L.
A prezentat raportul: RSF1_21
Pentru perioada fiscala: A/2023
Data prezentarii: 28.05.2024
Marca temporală a raportului înregistrat în Sistemul Informațional al BNS
: 29.05.2024 13:37:56

Biroul Național de Statistică (BNS) a recepționat varianta electronică a raportului, expediat de DVs. Urmează verificarea și validarea raportului de către specialistul BNS pe domeniu.

DECLARAŢIE
privind valabilitatea ofertei

Către: **CENTRUL PENTRU ACHIZITII PUBLICE CENTRALIZATE IN SANATATE**

Stimaţi domni,

Ne angajăm să menținem oferta valabilă, **Privind încheierea acordului-cadru - Achiziționarea dispozitivelor medicale conform Programului Naţional de combaterea hepatitelor virale B, C și D pentru anii 2025-2027,** pentru o durată de 160 zile, (una sută șase zeci), respectiv până la data de 25/02/2025 (ziua/luna/anul), și ea va rămâne obligatorie pentru noi și poate fi acceptată oricând înainte de expirarea perioadei de valabilitate.

Data completării 15.08.2024

Cu stimă,
Ofertant/candidat
Gabriela-Cristina Anghel
(semnătura autorizată)

MEDIST Grup S.R.L.
Str. Mitropolit Gavriil Bănulescu-Bodoni nr. 25
Oficiul 33, MD-2012 Chișinău, Rep. Moldova
Tel./Fax: +373 22 84 94 95
E-mail: office@medist.md
Web: www.medist.md

IDNO: 1018600004516
TVA: 0508191
BC Victoriabank SA, Filiala nr. 26 Chișinău
IBAN (MDL):MD57VI022242600000269MDL
SWIFT: VICBMD2X469

MEDIST Grup

Soluții pentru sănătate

DECLARAȚIE

Subsemnata Gabriela Anghel, reprezentant împuternicit al MEDIST GRUP S.R.L, cu sediul în mun. Chișinău, str. M.G. Bănulescu-Bodoni 25, Oficiul 33, declar pe propria răspundere că:

- termenul de valabilitate restant va constitui nu mai puțin de 80% din termenul total al produsului.
- livrarea produselor la destinatar se va efectua cu respectarea condițiilor de păstrare și transportare pe tot parcursul lanțului de transportare de la fabricant la beneficiar.
- mostrele (2 bucăți) vor fi prezentate în termen de 10 zile de la solicitare, ambalate și etichetate cu specificare obligatorie a modelului articolului, producătorului și țării de origine pe ambalajul original al mostrei. Mostrele vor fi prezentate în termen de 10 zile de la solicitare, într-o cutie pe care se va indica denumirea operatorului economic și numărul procedurii de achiziție publică. Se va prezenta lista mostrelor incluse în cutie și numărul de lot al acestora cu scrisoare de însoțire semnată. Pe fiecare produs în parte va fi indicat numărul lotului și denumirea operatorului economic.
- bunurile ce urmează a fi achiziționate sunt înregistrate în Registrul de Stat al Dispozitivelor Medicale, mai jos dovada:

REGISTRUL DE STAT AL DISPOZITIVELOR MEDICALE

Введите текст для поиска...

Nr	Denumire	Den.comerc.	Model	Nr. catalog	Tara	Producatorul	Reprezentant	Ordin	Data
						cepheid	medist		
DM000221904	TEST PENTRU DETERMINAREA HEPATITEI C	XPERT®	HCV VIRAL LOAD	GXHCV-VL-CE-10	Suedia	CEPHEID AB	MEDIST GRUP S.R.L.	Rg04-000173	23-07-2019
DM000221903	TEST PENTRU DETERMINAREA HEPATITEI B	XPERT®	HBV VIRAL LOAD	GXHBV-VL-CE-10	Suedia	CEPHEID AB	MEDIST GRUP S.R.L.	Rg04-000173	23-07-2019
DM000204993	TEST DE CALIBRARE PENTRU SISTEM AUTOMAT DE DIAGNOSTIC MOLECULAR	Xpert®	Check	XPERTCHECK-CE-5	SUA	CEPHEID	MEDIST GRUP S.R.L.	A07.PS-01.Rg04-91	05-04-2019

Data completării 15.08.2024

Cu stimă,

Ofertant/candidat

Gabriela-Cristina Anghel

(semnătura autorizată)

MEDIST Grup S.R.L.
Str. Mitropolit Gavriil Bănulescu-Bodoni nr. 25
Oficiul 33, MD-2012 Chișinău, Rep. Moldova
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IDNO: 1018600004516
TVA: 0508191
BC Victoriabank SA, Filiala nr. 26 Chișinău
IBAN (MDL):MD57VI022242600000269MDL
SWIFT: VICBMD2X469

Cepheid®

EC DECLARATION OF CONFORMITY

Manufacturer:

Cepheid AB
Röntgenvägen 5
SE-171 54 Solna
Sweden

Product name: Xpert® HCV Viral Load
Catalogue number(s): GXHCV-VL-CE-10

We, the manufacturer, hereby declare, under our sole responsibility, that the product(s) stated above conforms to Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices (IVDD), (LVFS 2001:7).

Product classification: Annex II, list A
Conformity Assessment route: Annex IV
Notified Body: BSI Group The Netherlands B.V.
Say Building, John M. Keynesplein 9
1066 EP Amsterdam
The Netherlands
Notified Body number: 2797
EC Certificate – Full Quality Assurance: CE 708525
EC Design-Examination Certificate: CE 708527

Signed on behalf of Cepheid AB by:

Signature
Lena Kirsel
Senior Manager of Regulatory Affairs

May 23, 2022
Date of Issue

Place of Issue: Solna, Sweden

Cepheid®

EC DECLARATION OF CONFORMITY

Manufacturer:

Cepheid AB
Röntgenvägen 5
SE-171 54 Solna
Sweden

Product name: Xpert® HBV Viral Load
Catalogue number(s): GXHBV-VL-CE-10

We, the manufacturer, hereby declare, under our sole responsibility, that the product(s) stated above conforms to Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices (IVDD), (LVFS 2001:7).

Product classification: Annex II, list A
Conformity Assessment route: Annex IV
Notified Body: BSI Group The Netherlands B.V.
Say Building, John M. Keynesplein 9
1066 EP Amsterdam
The Netherlands
Notified Body number: 2797
EC Certificate – Full Quality Assurance: CE 708525
EC Design-Examination Certificate: CE 708526

Signed on behalf of Cepheid AB by:

Signature
Lena Kirsel
Senior Manager of Regulatory Affairs

May 23, 2022
Date of Issue

Place of Issue: Solna, Sweden

EU DECLARATION OF CONFORMITY

	Cepheid 904 Caribbean Drive Sunnyvale, CA 94089 USA Single Registration Number (SRN): US-MF-000010979
EC REP	Cepheid Europe SAS Vira Solelh 81470 Maurens-Scopont France Single Registration Number (SRN): FR-AR-000001368
Device Trade Name	Xpert® Check
Basic UDI-DI	081164701-XPERTCHECK-3B
REF	XPERTCHECK-CE-5
Device Intended Purpose	**Intended Use** Xpert Check is part of a check, verification, and hardware test system for GeneXpert modules. Xpert Check is used in GeneXpert DX, GeneXpert Xpress and Infinity systems, and cannot be used in the GeneXpert Omni system. Xpert Check is used to check the optical system, verify the thermal system and perform a series of system-level tests to ensure full system functionality within Cepheid's instrument servicing specifications. One Xpert Check cartridge is usually used to check a single module in conjunction with the Xpert Check software. In certain cases where a retest is required, multiple cartridges may be necessary to test a module. **Intended User / Environment** Xpert Check is intended to be performed by trained users where a GeneXpert System is installed

We, as the manufacturer of the device take sole responsibility for and hereby declare that the above mentioned device meets the provisions of the following Regulation:

Regulation EU 2017/746 on *in vitro* Diagnostic Medical Devices				
Risk Class	A ☒	B☐	C☐	D☐
Classification Rule	Annex VIII, Implementing Rule 1.3. Accessory Annex VIII, Rule: 5 (b) Accessory to instrument			

Conformity Assessment Route	☐ Annex IX(I) Quality Management System ☐ Annex IX(II) Technical Documentation ☐ Annex X Type Examination ☐ Annex XI Production Quality Assurance ☒ Annex II & III (class A only)
Common Specification	Not applicable
Notified Body	Not applicable
Notified Body Number	Not appliable
Certificate(s)	Not applicable

Signed on behalf of Cepheid by:

Signature

November 2, 2022
Date of Issue

Lena Kirsel
Senior Manager of Regulatory Affairs
Regulatory Affairs

Place of Issue: Solna, Sweden

Cepheid®
A better way.

Simplify Hepatitis B Treatment Management

Xpert® HBV Viral Load

CE-IVD. *In Vitro* Diagnostic Medical Device. Not available in all countries. Not available in the United States.

“In order to expand treatment of Hepatitis B, simplified and easy to use core service interventions are needed to implement effective HBV DNA Testing. Xpert® HBV Viral Load has the potential to simplify disease management by offering a flexible workflow for any testing setting and quality results in approximately an hour.”

Professor Pietro Lampertico, MD, PhD
Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, Milan, Italy

The Goal

Elimination of Hepatitis by 2030

Viral hepatitis is one of the leading causes of death globally with 1.4 million deaths per year, as many as HIV/AIDS, tuberculosis or malaria. Hepatitis B and C viruses cause 95% of those deaths in the world.[1]

The WHO global health sector strategy to eliminate Viral Hepatitis as a major public health threat by 2030 requires considerable efforts from governments, healthcare authorities and communities.

Service delivery must be expanded to better manage the number of people living with Hepatitis B Virus (HBV).[1]

The Need

Efficient Treatment Delivery

- Although a vaccine for HBV exists, there is still no cure and lifelong treatment is needed for individuals already chronically infected with Hepatitis B Virus
- HBV rapid antibody testing is mainly done at point of care or in community based programmes but HBV viral load testing and monitoring is traditionally done in the laboratory with long turnaround times, which can result in more patients being lost to follow up and care
- Service coverage of core interventions are needed to expand prevention, testing and treatment for HBV

The Solution

Xpert HBV Viral Load on the GeneXpert® system

- Accurate and reliable quantification of HBV DNA in human serum or plasma
- Flexible thoughput for any testing setting with round the clock, on-demand results
- Simplify disease management with the possibility of having sample to viral load results less than one hour

Coverage, plus
Accuracy, plus
Peace of mind

That's the **PCR***plus* advantage.
From Cepheid.

The Impact

- **Improve Patient Care:** Same day results support better clinical decisions
- **Increase Efficiency:** High quality HBV viral load quantitative results for accurate treatment delivery
- **Patient Centered Diagnostics:** Simplify testing for multiple diseases using a single platform

Designed to simplify testing in low and high volume settings

No Waiting

- Deliver rapid individual patient results in a single visit

Simple and Organised

- True 24/7 random access accommodates other urgent test requests — i.e., Xpert® HCV Viral Load, Xpert® HIV-1 Viral Load, Xpert® MTB/RIF Ultra can run simultaneously on the same system

Improved Service

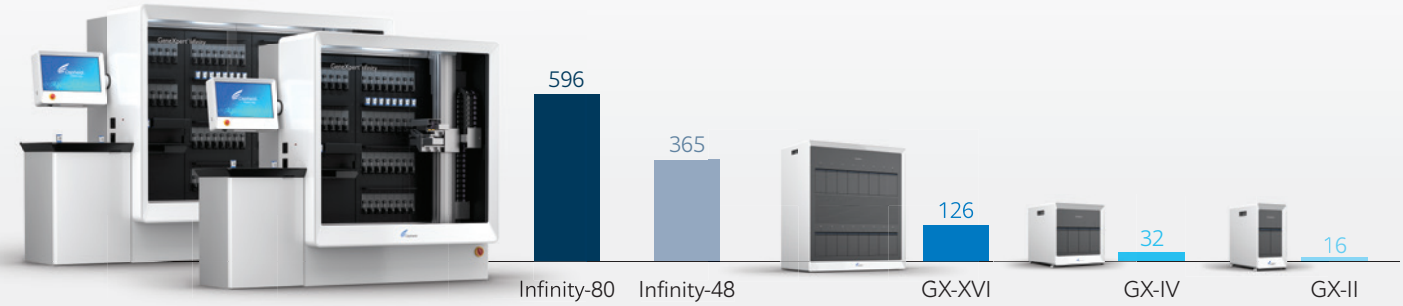
- Modular system can adapt to any throughput requirement from Health Clinics to National Reference Centers

Workflow: 2 Easy Steps

1 Transfer at least 0.6 mL of plasma or serum into the cartridge

2 Scan, load cartridge and start test

System Throughput* *8-hr shift*



* Operational throughput per 8-hr shift based on HBV Viral Load testing, internal analysis.

Catalog Information

Xpert® HBV Viral Load	10 tests	GXHBV-VL-CE-10

Reference:

1 WHO. Global Health Sector Strategy on Viral Hepatitis 2016–2021. 2016 June. Accessed Aug 2020. https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf;jsessionid=E5D2C86E67F6CAC0258DDC6892B5A5E8?sequence=1

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www.**Cepheidinternational**.com

WHO Prequalification of In Vitro Diagnostics
PUBLIC REPORT

Product: Xpert HCV Viral Load with GeneXpert Dx
GeneXpert Infinity-48s and
GeneXpert Infinity-80
WHO reference number: PQDx 0260-070-00

Xpert HCV Viral Load with **GeneXpert Dx, GeneXpert Infinity-48s**, and **GeneXpert Infinity-80, product code GXHCV-VL-CE-10** manufactured by **Cepheid AB, CE marked**, was accepted for the WHO list of prequalified in vitro diagnostics and was listed on 04 April 2017.

Summary of WHO prequalification assessment for Xpert HCV Viral Load

	Date	Outcome
PQ listing	04-Apr-2017	listed
Dossier review	N/A	MR
Site inspection(s) of quality management system	23 to 25-Jun-2015	MR
Product performance evaluation	2-Mar-2017	MR

MR: Meets requirements

N/A: Not applicable

Report amendments and/or product changes

This public report has since been amended. Amendments may have arisen because of changes to the prequalified product for which WHO has been notified and has undertaken a review. Amendments to the report are summarized in the following table, and details of each amendment are provided below.

Version	Summary of amendment	Date of report amendment
2.0	To reflect an acceptable commitment which resulted in the updated Intended Use in the instructions for use, and an accepted change in	27-Jun-2017

	specimen stability which resulted in updating labels and instructions for use, and the fulfilment of commitment to prequalification.	
3.0	Change of Cepheid's notified body from LRQA (UK) to BSI (Netherlands). Labels and IFUs were updated accordingly.	6-Jun-2019.
4.0	Addition of a new GeneXpert DX instrument product codes for use with all prequalified assays. New GeneXpert DX instrument models make use of GeneXpert modules which have a 10-channel optical system modules, compared to the 6-channel optical system that pre-existed.	3-Dec-2020

Intended use:

According to the claim of Cepheid AB, "*The HCV VL assay, performed on GeneXpert Instrument Systems, is designed for the rapid quantitation of Hepatitis C Virus (HCV) RNA in human serum or plasma (EDTA) from HCV-infected individuals. The test utilizes automated reverse transcriptase polymerase chain reaction (RT-PCR) using fluorescence to detect the RNA of interest for the quantitation of HCV. The HCV VL assay quantifies HCV genotypes 1–6 over the range of 10 to 100,000,000 IU/mL. The HCV VL assay is intended for use as an aid in the management of HCV infected patients undergoing antiviral therapy.*

The test measures HCV RNA levels at baseline and during treatment and can be utilized to predict sustained and non-sustained virological responses to HCV therapy.
Results from the HCV VL assay may also be used to confirm HCV infection in anti-HCV positive individuals. In anti-HCV positive individuals who test negative for HCV RNA, use of another HCV antibody assay may be considered for distinction between true HCV exposure and biologic false positivity. Repeat HCV RNA testing may be indicated in cases that have had HCV exposure in the last 6 months or have clinical evidence of HCV disease.

The assay is not intended to be used as a blood donor screening test for HCV".

Assay description:

According to the claim of Cepheid AB, "*GeneXpert Instrument Systems automate and integrate specimen purification, nucleic acid amplification, and detection of the target sequence in simple or complex specimens using real-time reverse transcriptase PCR (RT-PCR) which uses fluorescence to detect the RNA of interest. The systems consist of an instrument, personal computer, and preloaded software for running tests and viewing the results. The systems require the use of single-use disposable GeneXpert cartridges that hold the RT-PCR*

reagents and host the RT-PCR processes. Because the cartridges are self-contained, cross-contamination between samples is minimized.

For a full description of the system, see the GeneXpert Dx System Operator Manual or the GeneXpert Infinity System Operator Manual.

Xpert HCV Viral Load includes reagents for the detection of HCV RNA in specimens as well as two internal controls used for quantitation of HCV RNA. The internal controls monitor recovery and the presence of inhibitor(s) in the RT and PCR reactions. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability".

Test kit contents:

Xpert HCV Viral Load	**10 tests (product code GXHCV-VL-CE-10))**
Xpert HCV Viral Load cartridges with integrated reaction tubes	10
Disposable 1 mL transfer pipettes	1 bag of 10 per kit
CD (includes instructions for use)	1

Instrumentation:

Product name	**Product code**
GeneXpert Dx (including barcode scanner and operator manual)	GXI-1-L, GXI-1-D, GXII-1-L, GXII-1-D, GXII-2-L, GXII-2-D, GXIV-1-L, GXIV-1-D, GXIV-2-L, GXIV-2-D, GXIV-3-L, GXIV-3-D, GXIV-4-L, GXIV-4-D, GXXVI-4-L, GXXVI-4-D, GXXVI-8-L, GXXVI-8-D, GXXVI-12-L, GXXVI-12-D, GXXVI-16-L, GXXVI-16-D, GXI-1-D-10C GXIV-4-D-10C GXI-1-L-10C, GXIV-4-L-10C, GXII-1-D-10C GXXVI-4-D-10C, GXII-1-L-10C, GXXVI-4-L-10C GXII-2-D-10C, GXXVI-8-D-10C, GXII-2-L-10C GXXVI-8-L-10C, GXIV-1-D-10C, GXXVI-12-D-10C, GXIV-1-L-10C, GXXVI-12-L-10C, GXIV-2-D-10C, GXXVI-16-D-10C, GXIV-2-L-10C, GXXVI-16-L-10C, GXIV-3-D-10C, and GXIV-3-L-10C

GeneXpert Infinity-48s (including barcode scanner and operator manual)	INFINITY48-16, INFINITY48-16-EUROPE, INFINITY48-24, INFINITY48-24-EUROPE, INFINITY48-32, INFINITY48-32-EUROPE, INFINITY48-40, INFINITY48-40-EUROPE, INFINITY48-48, INFINITY48-48-EUROPE.
GeneXpert Infinity-80 (including barcode scanner and operator manual)	INFINITY80-16, INFINITY80-16-230V, INFINITY80-24, INFINITY80-24-230V, INFINITY80-32, INFINITY80-32-230V, INFINITY80-40, INFINITY80-40-230V, INFINITY80-48, INFINITY80-48-230V, INFINITY80-56, INFINITY80-56-230V, INFINITY80-64, INFINITY80-64-230V, INFINITY80-72, INFINITY80-72-230V, INFINITY80-80, INFINITY80-80-230V.
GeneXpert Dx Software Version 4.6a or higher (GeneXpert Dx systems); or Xpertise 6.2a or higher (Infinity-80/Infinity-48s)	GX4.0SWKIT, XPERTISE-G2-SWKIT

Items required but not provided:

Item
Consumables: Bleach or sodium hypochlorite 70% Ethanol Disposable gloves (one for each specimen processed) K2-EDTA specimen tubes EDTA Plasma Preparation Tubes (PPT) Serum collection tubes
Equipment: Printer (see Cepheid representative for additional information) Centrifuge for processing serum and plasma specimens

Storage:

The test kit (Xpert HCV Viral Load) should be stored at 2 to 28 °C).

Shelf-life upon manufacture:

12 months.

Warnings/limitations:
Please refer to current version of manufacturer's instructions for use

Prioritization for prequalification
Based on the established eligibility criteria, Xpert HCV Viral Load was given priority for WHO prequalification assessment.

Product dossier assessment

In accordance with the WHO procedure for abbreviated prequalification assessment, Cepheid AB was not required to submit a product dossier for Xpert HCV Viral Load as per the "*Instructions for compilation of a product dossier*" (PQDx_018 v1). Notwithstanding, certain aspects of the product dossier previously submitted for stringent regulatory review were reviewed by an assessor during the site inspection.

Manufacturing site inspection

In accordance with the WHO procedure for abbreviated prequalification assessment, a shortened inspection with fewer inspectors was conducted at the site(s) of manufacture Röntgenvägen 5, SE-171 54 Solna, Sweden of Xpert HCV Viral Load between 23 and 25 June 2015[1] as per the "*Information for manufacturers on prequalification inspection procedures for the sites of manufacture of diagnostics*" (PQDx_014 v1).

The inspection found that the manufacturer had an acceptable quality management system and good manufacturing practices in place that ensured the consistent manufacture of a product of good quality.

The manufacturer's responses to the nonconformities found at the time of the inspection were accepted 23 May 2016.
Based on the site inspection and corrective action plan review, the quality management system for Xpert HCV Viral Load with GeneXpert Dx, GeneXpert Infinity-48s and GeneXpert Infinity-80 meets WHO prequalification requirements.

[1] Sites at 904 Caribbean Drive, Sunnyvale 94089-1189, California, USA and 1339 Moffet Park Drive, Sunnyvale 94089, California, USA were also inspected on 29 to 30 June 2015.

To note:
Due to the COVID-19 pandemic and the corresponding national and international travel restriction some inspection dates may be impacted.

Please see below the link to the official statement of the PQ team regarding the impact of COVID-19 on Prequalification activities:
https://www.who.int/diagnostics_laboratory/eual/impact_covid-19_PQT/en/

Product performance evaluation

Xpert HCV Viral Load is intended for use in human EDTA plasma /serum specimens. A volume of 1000µl of specimen is needed to perform the assay. This type of assay requires general laboratory equipment such as centrifuge, vortex as well as continuous electricity and cannot be performed in laboratories with limited facilities.

The limit of detection (LOD) of the assay was confirmed at 4.91 IU/mL (95% CI: 3.17 to 10.69 IU/mL) using the 5th WHO International Standard for HCV NAT (NIBSC code: 14/150).

All genotypes present in the 4th HCV RNA Genotype Panel for Nucleic Acid Amplification (NIBSC code: 14/290) were detected. Fourteen of the 15 specimens in the NRL HCV RNA Mixed Genotype Panel were detected; one specimen (Genotype 2) was invalid on initial and repeat testing.

In this limited performance evaluation on a panel of 102 clinical specimens, we found an initial bias (95% CI) of -0.135 (-0.1839 to -0.0859) compared to the reference results. The sensitivity (95% CI) was 100% (94.6% to 99.9%) and a specificity (95% CI) of 100% (75.9 % to 99.4%) compared to the reference results.

In this study, the invalid rate was 0.48% and the error rate was 1.67%.

Performance characteristics in comparison with an agreed reference standard	
	Initial estimate (95% CI)
Sensitivity %	100% (94.6 to 99.9%)
Specificity %	100% (75.9 to 99.4%)
Invalid rate %	0.48%
Error rate %	1.67%

Additional performance characteristics	
Genotype detection	All genotypes present in the 4th HCV RNA Genotype Panel for Nucleic Acid Amplification (NIBSC code: 14/290) were detected. 14/15 specimens in the NRL HCV RNA Mixed Genotype Panel were detected.
Limit of detection using 5th WHO International Standard for HCV NAT (NIBSC code: 14/150)	4.91 IU/mL (95% CI: 3.17 to 10.69 IU/mL)
Cross-contamination	0%

Key operational characteristics	
Validated specimen types	EDTA plasma, serum
Number of steps	2
Time to result	1 hour: 45 minutes
Internal QC	Sample Processing Control (SPC): Armored RNA® in the form of a dry bead that is included in each cartridge to verify adequate processing of the sample virus.
In-use stability of reagents	Reagents are all contained within the cartridge. Cartridges must be tested maximum 30 minutes after addition of specimen.

Labelling

1. **Labels**
2. **Instructions for use**

1. Labels

Figure 1: kit carton label

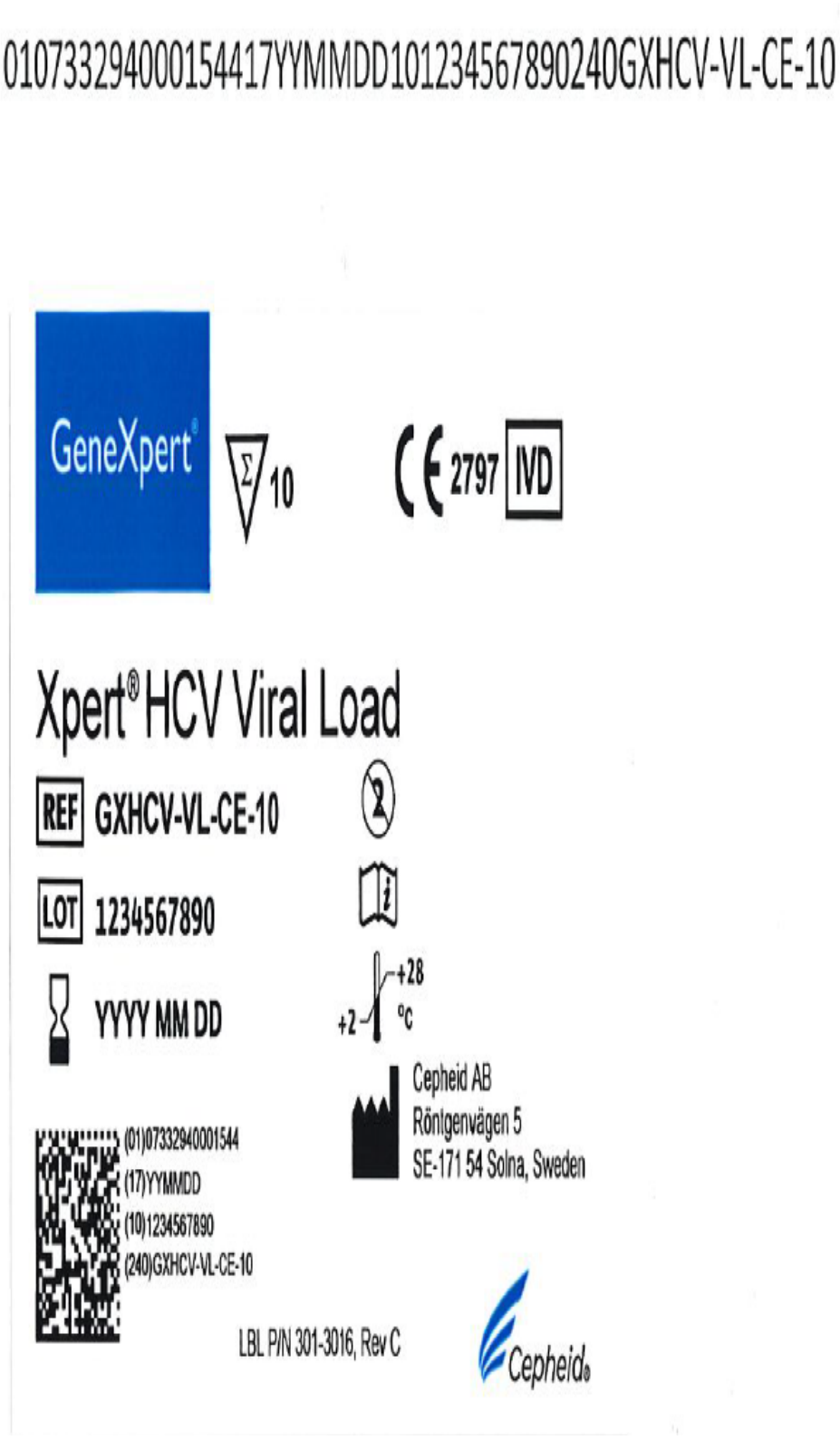


Figure 2: kit corner label

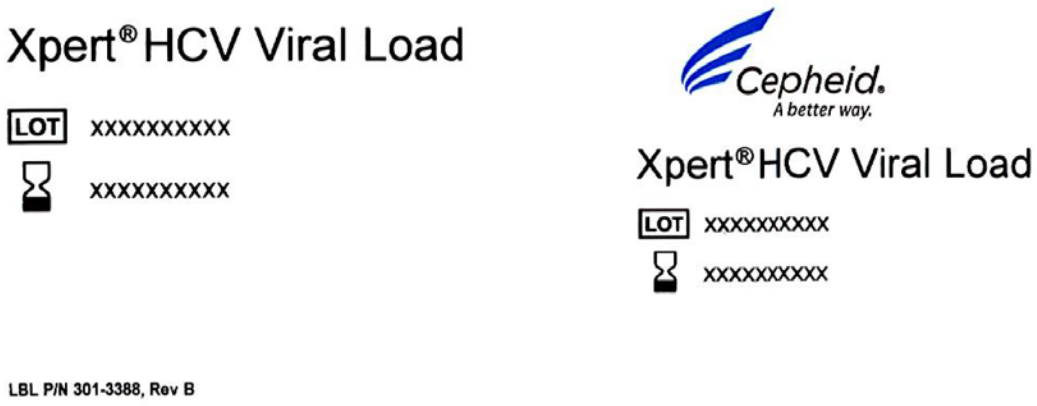
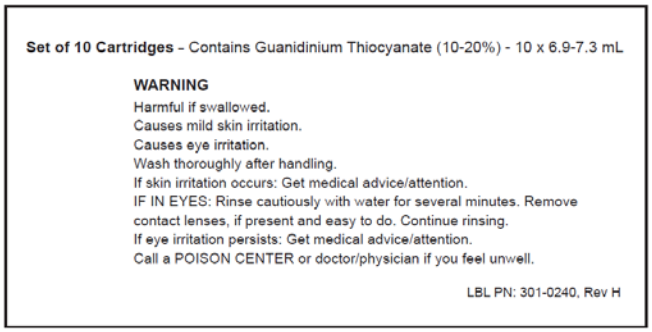


Figure 3: kit hazard label

HCV VL, HIV Qual and HIV VL 10-Test Kits
Set of 10 Cartridges - Guanidinium Thiocyanate (10-20%) - 6.9-7.3 mL
Hazard Warning Label
Updated 04/20/18



Stock Label p/n 301-0240, Rev H

Material:	Transtherm 1C Paper
Colors:	Black
Adhesive:	AT20
Topcoat:	Full UV Varnish
Label Size:	4.0” x 2.0”
Copy Unwind Position:	#4
General Specifications:	Reference Cepheid Doc D7280 for additional requirements

Figure 4: cartridge label

2. Instructions for use[2]

[2] English version of the IFU was the one that was assessed by WHO. It is the responsibility of the manufacturer to ensure correct translation into other languages.

GeneXpert
Powered By CEPHEID INNOVATION

Xpert® HCV Viral Load

REF **GXHCV-VL-CE-10**

GXHCV-VL-IN-10

Cepheid *In Vitro* Diagnostic Medical Device CE 2797 IVD

301-3019, Rev. F March 2019

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Cepheid AB
Röntgenvägen 5
SE-171 54 Solna
Sweden

Xpert® HCV Viral Load

For *In Vitro* Diagnostic Use Only.

1 Proprietary Name

Xpert® HCV Viral Load

2 Common or Usual Name

HCV VL

3 Intended Use

The HCV VL assay, performed on GeneXpert® Instrument Systems, is designed for the rapid quantitation of Hepatitis C Virus (HCV) RNA in human serum or plasma (EDTA) from HCV-infected individuals. The test utilizes automated reverse transcriptase polymerase chain reaction (RT-PCR) using fluorescence to detect the RNA of interest for the quantitation of HCV.

The HCV VL assay quantifies HCV genotypes 1–6 over the range of 10 to 100,000,000 IU/mL. The HCV VL assay is intended for use as an aid in the management of HCV infected patients undergoing antiviral therapy. The test measures HCV RNA levels at baseline and during treatment and can be utilized to predict sustained and nonsustained virological responses to HCV therapy.

Results from the HCV VL assay may also be used to confirm HCV infection in anti-HCV positive individuals. In anti-HCV positive individuals who test negative for HCV RNA, use of another HCV antibody assay may be considered for distinction between true HCV exposure and biologic false positivity. Repeat HCV RNA testing may be indicated in cases that have had HCV exposure in the last 6 months or have clinical evidence of HCV disease.

The assay is not intended to be used as a blood donor screening test for HCV.

4 Summary and Explanation

HCV is a member of the Flaviviridae family and has been recognized as the major causative agent of chronic liver disease, including chronic active hepatitis, cirrhosis and hepatocellular carcinoma.[1] The HCV genome is a positive-sense RNA molecule of approximately 9500 nucleotides.[1] HCV is usually transmitted through percutaneous exposure to infected blood, primarily by intravenous drug use and receipt of unscreened donated blood products. Less frequently, HCV has been shown to be transmitted through occupational, perinatal and sexual exposures.[2]

An estimated 185 million people, or roughly 3% of the world's population, have been infected with HCV, and over 80% live in Low and Middle Income Countries (LMICs).[3] The burden of disease is greatest in developing countries; the highest reported prevalence is in China (3.2%)[4] Pakistan (4.8%)[4], Nigeria (18.3%)[5] and Egypt (22%).[4] About 15 million European adults are infected with HCV and most of these people are unaware of their infection.[6] Each year, 350,000 to 500,000 people die from HCV-related liver disease.[7]

Antiviral medicines can cure HCV, but access to diagnosis and treatment is low.[7] A cure for HCV infection is now possible in most patients with highly effective, safe and tolerable combinations of oral direct-acting antivirals (DAAs) taken for 8–24 weeks.[5] Eradication of HCV is being discussed for the first time.[5]

Quantitation of HCV RNA has proven useful in providing a metric to evaluate the effectiveness of antiviral response to HCV treatment. Guidelines for the management and treatment of HCV recommend quantitative testing for HCV RNA before the start of antiviral therapy, during therapy, and after the conclusion of treatment. The primary objective of treatment is Sustained Virologic Response (SVR), defined as undetectable HCV RNA by a sensitive test 12 or 24 weeks after the end of treatment depending on the anti-HCV therapy.[8]

5 Principle of the Procedure

The GeneXpert Instrument Systems automate and integrate sample purification, nucleic acid amplification, and detection of the target sequence in simple or complex samples using RT-PCR which uses fluorescence to detect the RNA of interest. The systems consist of an instrument, personal computer, and preloaded software for running tests and viewing the results. The systems require the use of single-use disposable GeneXpert cartridges that hold the RT-PCR reagents and host the RT-PCR processes. Because the cartridges are self-contained, cross-contamination between samples is minimized. For a full description of the systems, refer to the appropriate *GeneXpert Dx Operator Manual* or *GeneXpert Infinity Operator Manual*.

The HCV VL assay includes reagents for the detection of HCV RNA in specimens as well as two internal controls used for quantitation of HCV RNA. The internal controls monitor recovery and the presence of inhibitor(s) in the RT and PCR reactions. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

6 Reagents

6.1 Materials Provided

The HCV VL assay kit contains sufficient reagents to process 10 specimens or quality control samples. The kit contains the following:

HCV VL Assay Cartridges with Integrated Reaction Tubes	**10**
• Bead 1, Bead 2, and Bead 3 (freeze-dried)	1 of each per cartridge
• Lysis Reagent (Guanidinium Thiocyanate)	2.0 mL per cartridge
• Rinse Reagent	0.5 mL per cartridge
• Elution Reagent	1.5 mL per cartridge
• Binding Reagent	2.4 mL per cartridge
• Proteinase K Reagent	0.48 mL per cartridge
Disposable 1 mL Transfer Pipettes	**10 per kit**
CD	**1 per kit**
• Assay Definition File (ADF)	
• Instructions to import ADF into GeneXpert software	
• Instructions for Use (Package Insert)	

Note Safety Data Sheets (SDS) are available at www.cepheidinternational.com under the **SUPPORT** tab.

Note The bovine serum albumin (BSA) in the beads within this product was produced and manufactured exclusively from bovine plasma sourced in the United States. No ruminant protein or other animal protein was fed to the animals; the animals passed ante- and post-mortem testing. During processing, there was no mixing of the material with other animal materials.

7 Storage and Handling

- Store the HCV VL assay cartridges and reagents at 2–28 °C.
- Do not open the cartridge until you are ready to perform the assay.
- Do not use a cartridge that has leaked.
- Do not use HCV VL assay cartridges and reagents that were previously frozen.
- Do not use reagents or cartridges that have passed the expiration date.

8 Materials Required but Not Provided

- GeneXpert Dx System or GeneXpert Infinity Systems (catalog number varies by configuration): GeneXpert Instrument, computer with proprietary GeneXpert Dx Software Version 4.7b or higher (GeneXpert Dx systems); or Xpertise 6.4b or higher (Infinity-80/Infinity-48s), barcode scanner, and operator manual.
- Printer: If a printer is needed, contact Cepheid Technical Support to arrange for the purchase of a recommended printer.
- Bleach or sodium hypochlorite

9 Warnings and Precautions

- Treat all biological specimens, including used cartridges, as if capable of transmitting infectious agents. Because it is often impossible to know which might be infectious, all biological specimens should be treated with standard precautions. Guidelines for specimen handling are available from the U.S. Centers for Disease Control and Prevention[9] and the Clinical and Laboratory Standards Institute.[10]
- Good laboratory practices and changing gloves between handling specimens are recommended to avoid contamination of specimens or reagents.
- Follow your institution's safety procedures for working with chemicals and handling biological samples.
- Do not substitute HCV VL assay reagents with other reagents.
- Do not open the HCV VL assay cartridge lid except when adding sample.
- Do not use a cartridge that has been dropped after removing it from the packaging.
- Do not shake the cartridge. Shaking or dropping the cartridge after opening the lid may yield invalid results.
- Do not use a cartridge that has a damaged reaction tube.
- Do not use a cartridge that has leaked.
- Each single-use HCV VL assay cartridge is used to process one test. Do not reuse cartridges.
- The single-use disposable pipette is used to transfer one specimen. Do not reuse spent disposable pipettes.
- Wear clean lab coats and gloves. Change gloves between processing each sample.
- In the event of contamination of the work area or equipment with samples or controls, thoroughly clean the contaminated area with a solution of 1:10 dilution of household chlorine bleach or sodium hypochlorite and then 70% ethanol or 70% denatured ethanol. Wipe work surfaces dry completely before proceeding.
- Consult your institution's environmental waste personnel on proper disposal of used cartridges and unused reagents. Check state, territorial, or local regulations as they may differ from national disposal regulations. The material may exhibit characteristics of hazardous waste requiring specific disposal requirements. Institutions should check their hazardous waste disposal requirements.
- Biological specimens, transfer devices, and used cartridges should be considered capable of transmitting infectious agents requiring standard precautions. Follow your institution's environmental waste procedures for proper disposal of used cartridges and unused reagents. These materials may exhibit characteristics of chemical hazardous waste requiring specific disposal. If country or regional regulations do not provide clear direction on proper disposal, biological specimens and used cartridges should be disposed per WHO [World Health Organization] medical waste handling and disposal guidelines.

10 Chemical Hazards[11,12]

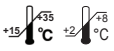
- Signal Word: WARNING
- **UN GHS Hazard Statements:**
  - Harmful if swallowed
  - Causes mild skin irritation
  - Causes eye irritation
- **UN GHS Precautionary Statements:**
  - **Prevention:**
    - Wash thoroughly after handling.
  - **Response:**
    - Call a POISON CENTER of doctor/physician if you feel unwell.
    - If skin irritation occurs: Get medical advice/attention.
    - IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses if present and easy to do. Continue rinsing.
    - If eye irritation persists: Get medical advice/attention.

11 Specimen Collection, Storage, and Transport

Whole blood should be collected in K2-EDTA tubes, EDTA-PPT or serum collection tubes and centrifuged to separate the plasma/serum and red blood cells per the manufacturer's instructions.

- A minimum of 1 mL plasma or serum is required for the HCV VL assay. If using the transfer pipette included in the kit, a minimum of 1.2 mL plasma or serum is required. Alternatively, if using a precision pipette, a minimum of 1 mL plasma or serum is required.

- Whole blood may be held at 15–30 °C for up to 24 hours or at 2–8 °C for up to 3 days prior to plasma/serum preparation. Centrifugation should be performed according to the manufacturer instructions.



- After centrifugation and separation, plasma and serum may be held at 15–35 °C for up to 24 hours or at 2–8 °C for up to 3 days prior to testing.

- Plasma and serum specimens are stable frozen (-70 to -18 °C) for 6 weeks.
- Plasma and serum specimens are stable for up to three freeze/thaw cycles.
- Plasma and serum specimens must be thawed and equilibrated to room temperature prior to transfer to the cartridge.

- Ship whole blood, plasma or serum specimens at 2–8 °C.
- Transportation of whole blood, plasma or serum specimens must comply with country, federal, state and local regulations for the transportation of etiologic agents.

12 Procedure

12.1 Preparing the Specimen

1. Following centrifugation of whole blood samples, 1 mL of plasma can be pipetted directly into the cartridge. Sufficient volume is critical to obtaining valid test results (see instructions in Section 12.2, Preparing the Cartridge Option 1 below).

2. If using frozen specimens, place the specimens at room temperature (20–35 °C) until completely thawed and equilibrated to room temperature before use.

3. Plasma and serum samples stored at 2–8 °C should be removed from the refrigerator and equilibrated to room temperature before use.

4. Plasma samples stored at 2–8 °C or frozen and thawed should be vortexed for 15 seconds before use, if the specimen is cloudy, clarify by a quick centrifugation.

12.2 Preparing the Cartridge

1. Wear protective disposable gloves.
2. Inspect the test cartridge for damage. If damaged, do not use it.
3. Open the lid of the test cartridge.

- **Option 1**: If using the transfer pipette included in the kit (Figure 1), fill to just below the bulb but above the line to transfer at least 1 mL plasma or serum from the collection tube into the sample chamber of the test cartridge (Figure 2). Do **NOT** pour the specimen into the chamber!
- **Option 2**: If using an automatic pipette, transfer at least 1 mL of plasma or serum into the sample chamber of the test cartridge (Figure 2). Do **NOT** pour the specimen into the chamber!

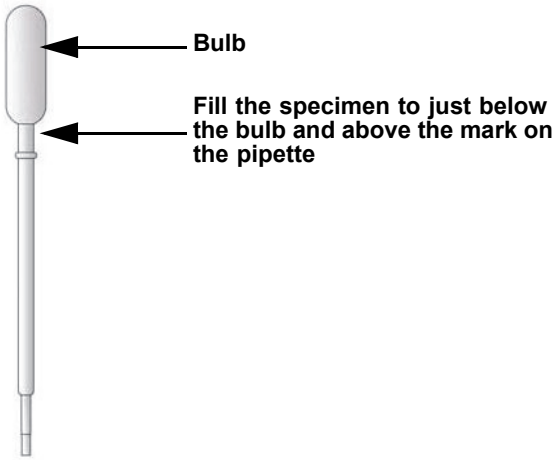


Figure 1. HCV VL Assay Transfer Pipette

4. Close the cartridge lid.
5. Load the cartridge into the GeneXpert Dx instrument or Infinity system.

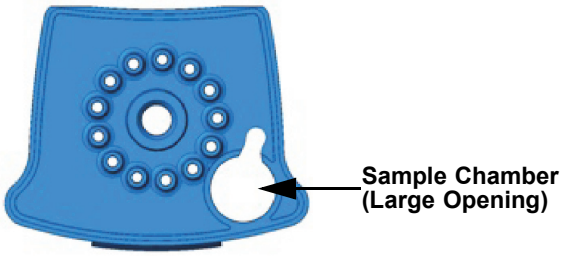


Figure 2. HCV VL Assay Cartridge (Top View)

12.3 Starting the Test

Important **Before you start the test, make sure the HCV VL Assay Definition File (ADF) is imported into the software.**

Note The steps you follow can be different if the system administrator changed the default workflow of the system.

This section lists the basic steps for running the test. For detailed instructions, see the *GeneXpert Dx System Operator Manual* or the *GeneXpert Infinity System Operator Manual*, depending on the model that is being used.

1. Turn on the GeneXpert instrument:
   - If using the GeneXpert Dx instrument, first turn on the instrument and then turn on the computer. The GeneXpert software will launch automatically. If it doesn't, double-click the GeneXpert Dx software shortcut icon on the Windows® desktop.

     or

   - If using the GeneXpert Infinity instrument, power up the instrument. The GeneXpert software will launch automatically. If it doesn't, double-click the Xpertise software shortcut icon on the Windows® desktop.
2. Log on to the GeneXpert Instrument System software using your user name and password.
3. In the GeneXpert System window, click **Create Test** (GeneXpert Dx) or **Orders** and **Order Test** (Infinity).
4. Scan in the Patient ID (optional). If typing the Patient ID, make sure the Patient ID is typed correctly. The Patient ID is associated with the test results and is shown in the View Results window.
5. Scan or type in the Sample ID. If typing the Sample ID, make sure the Sample ID is typed correctly. The Sample ID is associated with the test results and is shown in the View Results window and all reports. The Scan Cartridge dialog box appears.
6. Scan the barcode on the HCV VL assay cartridge. The Create Test window appears. Using the barcode information, the software automatically fills the boxes for the following fields: Select Assay, Reagent Lot ID, Cartridge SN, and Expiration Date.
7. Click **Start Test** (GeneXpert Dx) or **Submit** (Infinity). Enter your password, if requested.
8. For the GeneXpert Infinity System, place the cartridge on the conveyor belt. The cartridge will be automatically loaded, the test will run, and the used cartridge will be placed into the waste container.

   or

   For the GeneXpert Dx Instrument:

   A. Open the instrument module door with the blinking green light and load the cartridge.

   B. Close the door. The test starts and the green light stops blinking. When the test is finished, the light turns off.

   C. Wait until the system releases the door lock before opening the module door and removing the cartridge.

   D. The used cartridges should be disposed in the appropriate specimen waste containers according to your institution's standard practices.

13 Viewing and Printing Results

This section lists the basic steps for viewing and printing results. For more detailed instructions on how to view and print the results, see the *GeneXpert Dx System Operator Manual* or the *GeneXpert Infinity System Operator Manual*, depending on the instrument used.

1. Click the **View Results** icon to view results.
2. Upon completion of the test, click the **Report** button of the View Results window to view and/or generate a PDF report file.

14 Quality Control

CONTROL

Each test includes a Sample Volume Adequacy (SVA), Internal Quantitative Standard High and Low (IQS-H and IQS-L, also acts a specimen processing control [SPC]) and Probe Check Control (PCC).

- **Sample Volume Adequacy (SVA) –** Ensures the sample was correctly added to the cartridge. The SVA verifies that the correct volume of sample has been added in the sample chamber. The SVA passes if it meets the validated acceptance criteria. If the SVA does not pass, an **ERROR 2096** will be displayed if there is no sample or an **ERROR 2097** will be displayed if there is not enough sample. The system will prevent the user from resuming the test.
- **Internal Quantitative Standard High and Low (IQS-H and IQS-L) –** IQS-H and IQS-L are two Armored RNA® constructs in the form of a dry bead that goes through the whole assay process. The IQS-H and IQS-L are standards calibrated against the WHO 4th International standard for HCV. They are used for quantification by using lot specific parameters for the calculation of HCV RNA concentration in the sample. Additionally IQS-H and IQS-L detect specimen-associated inhibition of the RT-PCR reaction. The IQS-H and IQS-L pass if they meet the validated acceptance criteria.
- **Probe Check Control (PCC)** – Before the start of the PCR reaction, the GeneXpert Instrument System measures the fluorescence signal from the probes to monitor bead rehydration, reaction tube filling, probe integrity and dye stability. The PCC passes if it meets the validated acceptance criteria.
- **External Controls –** Following good laboratory practices, external controls, not available in the kit, should be used in accordance with local, state, and federal accrediting organizations' requirements as applicable.

15 Interpretation of Results

The results are interpreted automatically by the GeneXpert Instrument System from measured fluorescent signals and embedded calculation algorithms and are clearly shown in the View Results window (Figure 3 and Figure 5). Possible results are shown in Table 1.

Table 1. HCV VL Assay Results and Interpretation

Result	Interpretation
HCV DETECTED **XX IU/mL (log X.XX)** See Figure 3.	The HCV RNA is detected at XX IU/mL. • The HCV RNA has a titer within the linear range setting of the assay and the endpoint above the minimum. • IQS-H and IQS-L: PASS. • Probe Check: PASS; all probe check results pass.
HCV DETECTED **> 1.00E08 IU/mL** See Figure 4.	The HCV RNA is detected above the quantitative range of the assay. • IQS-H and IQS-L: PASS. • Probe Check: PASS; all probe check results pass.
HCV DETECTED **< 10 IU/mL** See Figure 5.	The HCV RNA is detected below the quantitative range of the assay. • IQS-H and IQS-L: PASS. • Probe Check: PASS; all probe check results pass.
HCV NOT DETECTED See Figure 6.	The HCV RNA is not detected. • HCV RNA is not detected. • IQS-H and IQS-L: PASS. • Probe Check: PASS; all probe check results pass.
INVALID See Figure 7.	Presence or absence of the HCV RNA cannot be determined. Repeat test according to the instructions in Section 16.2, Retest Procedure. • IQS-H and/or IQS-L: FAIL; Cycle thresholds (Cts) are not within valid range and the endpoint is below the minimum setting. • Probe Check: PASS; all probe check results pass.

Table 1. HCV VL Assay Results and Interpretation (Continued)

Result	Interpretation
ERROR See Figure 8.	Presence or absence of HCV RNA cannot be determined. Repeat test according to the instructions in Section 16.2, Retest Procedure. • Probe Check: FAIL*; all or one of the probe check results fail. * If the probe check passed, the error is caused by the maximum pressure limit exceeding the acceptable range or by a system component failure.
NO RESULT	Presence or absence of HCV RNA cannot be determined. Repeat test according to the instructions in Section 16.2, Retest Procedure. A **NO RESULT** indicates that insufficient data were collected. For example, the operator stopped a test that was in progress.

Note Assay screenshots are for example only. Assay name and version number may vary from the screenshots shown in this package insert.

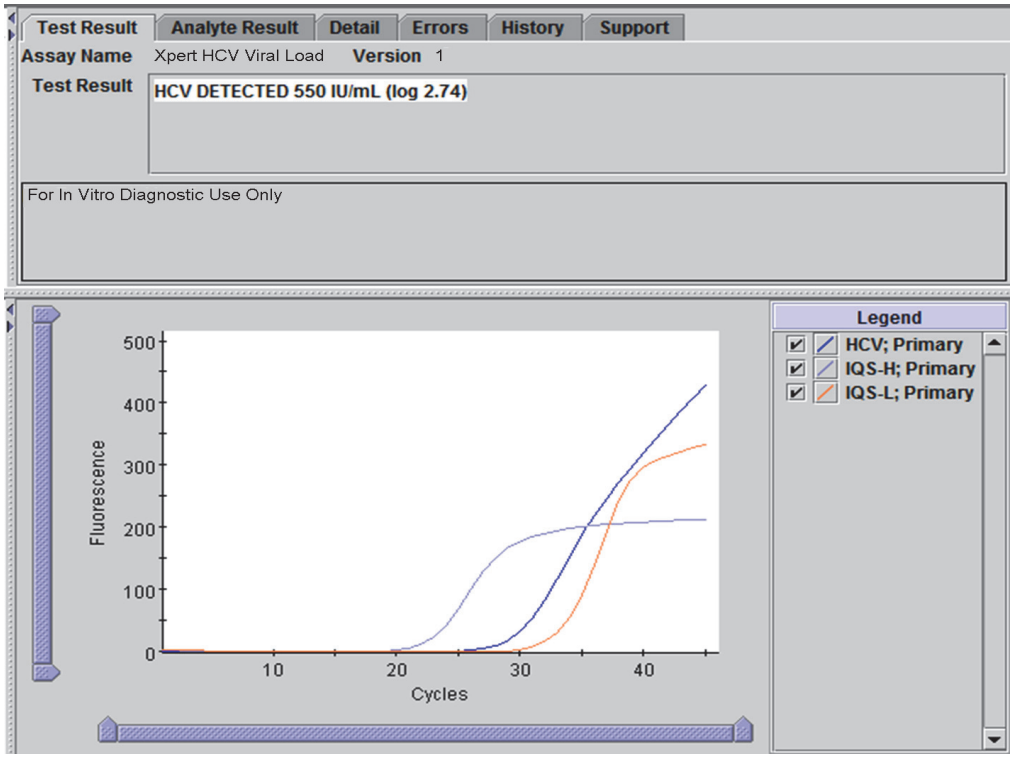


Figure 3. HCV Detected and Quantified

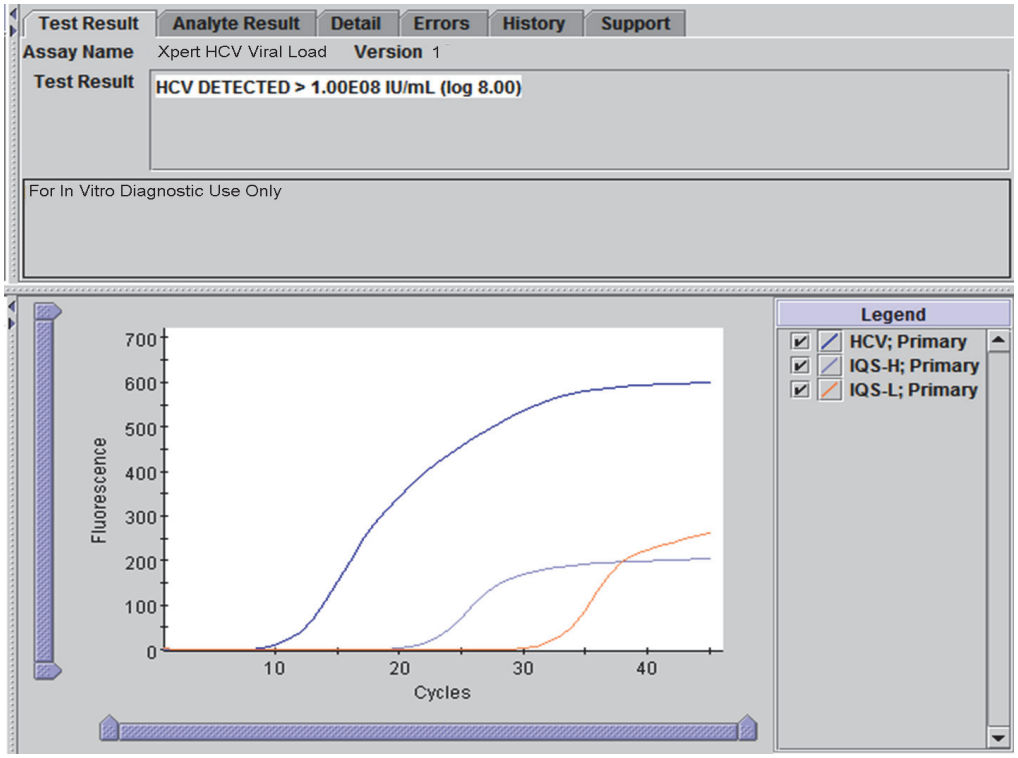


Figure 4. HCV Detected

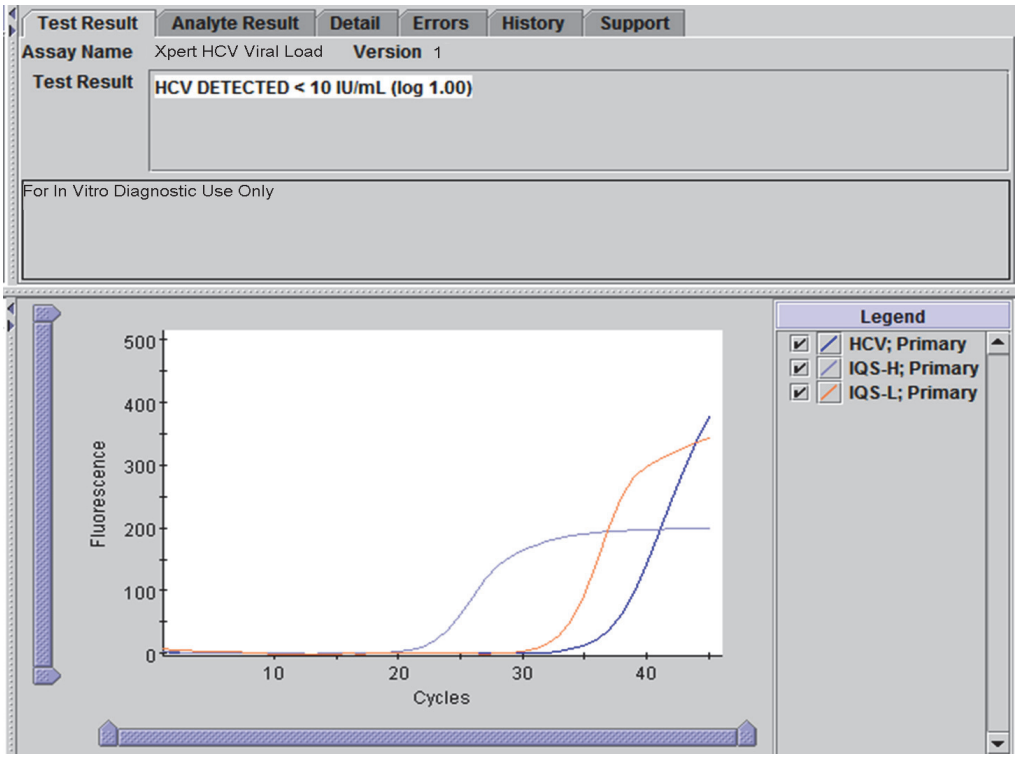


Figure 5. HCV Detected

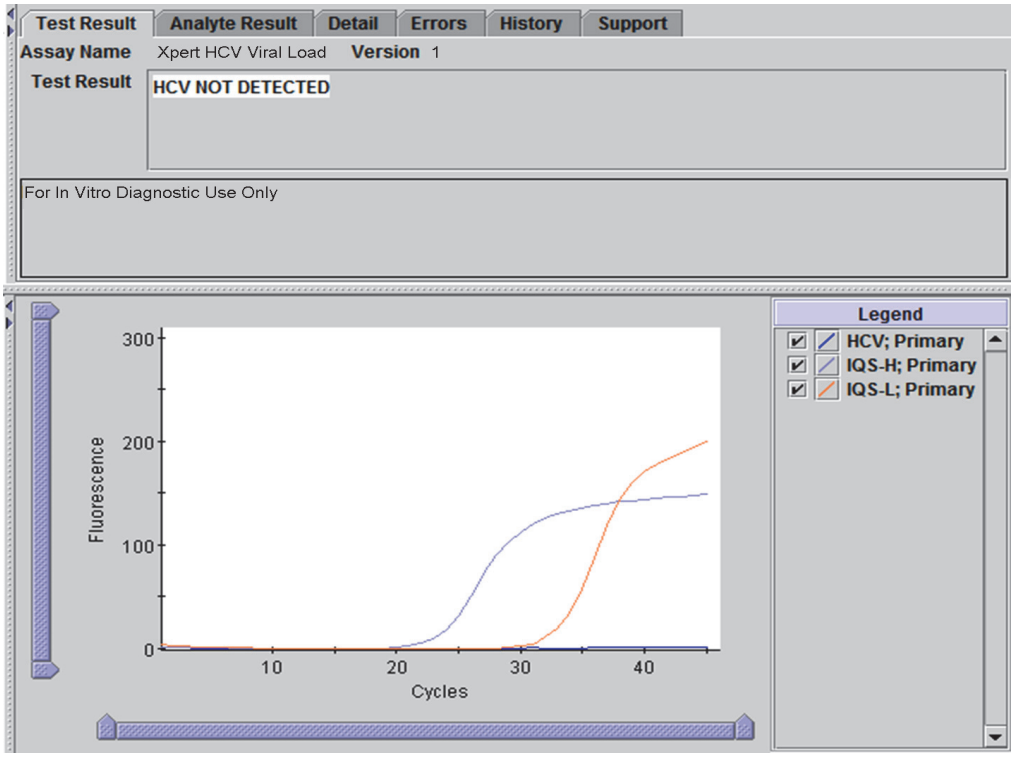


Figure 6. HCV Not Detected

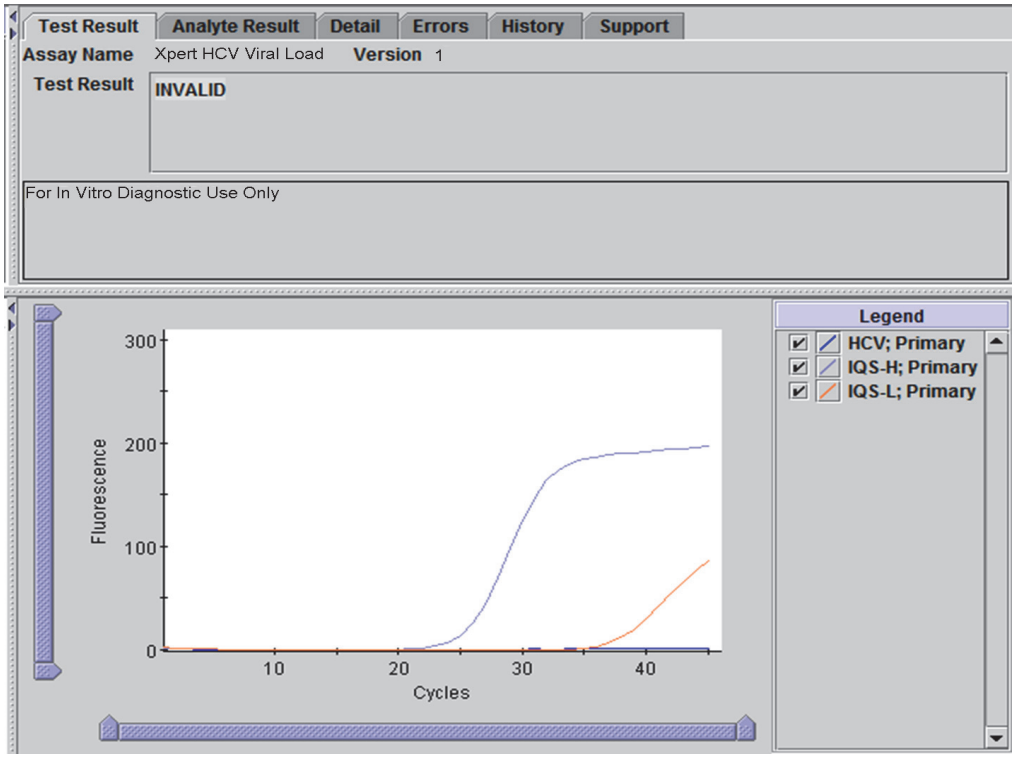


Figure 7. Invalid

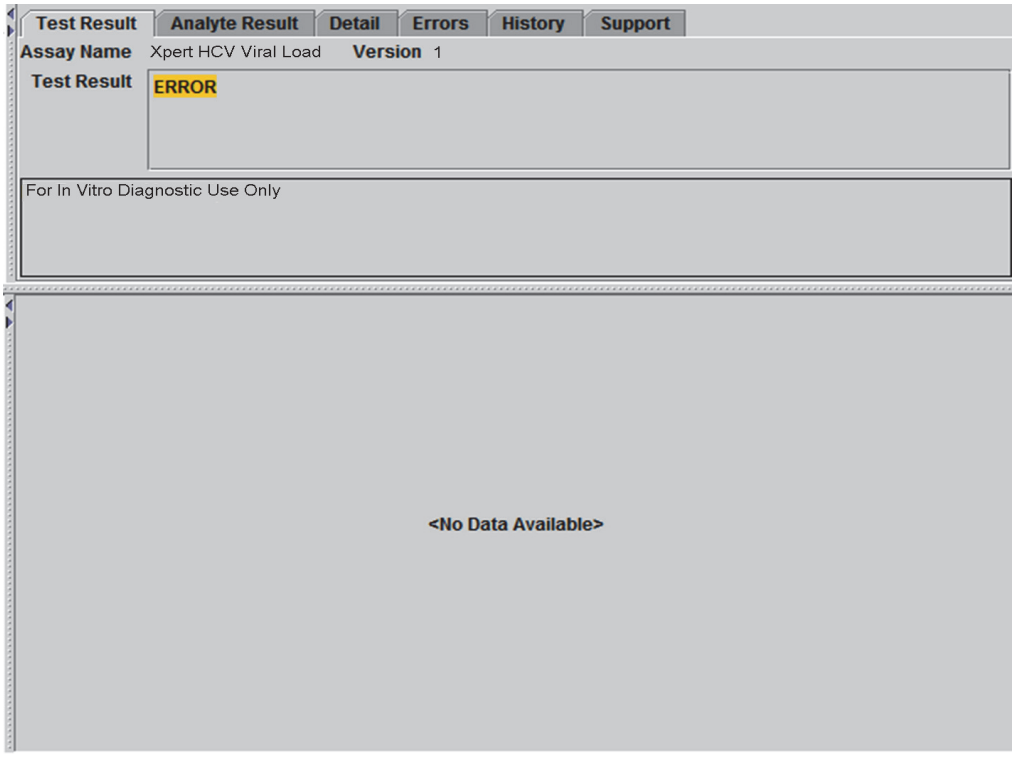


Figure 8. Error

16 Retests

16.1 Reasons to Repeat the Assay

If any of the test results mentioned below occur, repeat the test according to the instructions in Section 16.2, Retest Procedure.

- An **INVALID** result indicates one or more of the following:
  - The IQS-H and/or IQS-L Cts are not within valid range.
  - The sample was not properly processed or PCR was inhibited.
- An **ERROR** result indicates that the assay was aborted. Possible causes include: insufficient volume of sample was added, the reaction tube was filled improperly, a reagent probe integrity problem was detected, or the maximum pressure limit was exceeded.
- A **NO RESULT** indicates that insufficient data were collected. For example, the operator stopped a test that was in progress, or a power failure occurred.

16.2 Retest Procedure

For retest of a **NO RESULT**, **INVALID**, or **ERROR** result, use a new cartridge (do not re-use the cartridge) and new reagents.

1. Remove a new cartridge from the kit.
2. See Section 12, Procedure, including Section 12.1, Preparing the Specimen, Section 12.2, Preparing the Cartridge, and Section 12.3, Starting the Test.

17 Limitations

Good laboratory practices and changing gloves between handling specimens are recommended to avoid contamination of reagents.

Mutations or polymorphisms in primer or probe binding regions may affect detection of new or unknown HCV variants resulting in a false negative result.

18 Performance Characteristics

18.1 Limit of Detection

The limit of detection (LOD) of the HCV VL assay was determined by testing eight different dilutions prepared from a HCV genotype 1 reference standard in HCV negative EDTA plasma and serum. The HCV genotype 1 material used in the LOD study was the WHO 4th International standard, NIBSC code 06/102. The limit of detection was determined for three reagent lots and a total of 72 or 73 replicates per concentration level were tested. One additional low concentration level was included for both sample types after the first day of testing. The number of tested replicates for this level was thus smaller (49 in plasma and 53 in serum). The evaluation was performed according to CLSI guideline E17-A2. The HCV RNA concentration that can be detected with a positivity rate of greater than 95% was determined by Probit regression analysis and the results for the individual lots and specimens are shown in Table 2. The maximum observed LOD with Probit analysis for HCV genotype 1 in EDTA plasma is 4.0 IU/mL (95% CI 2.8 – 5.2). The maximum observed LOD with Probit analysis for HCV genotype 1 in serum is 6.1 IU/mL (95% CI 4.2 – 7.9).

Table 2. HCV VL LOD Estimates with Probit Regression and 95% Upper and Lower Confidence Intervals for HCV Genotype 1 Specimens in Plasma and Serum per Kit Lot

Specimen	Lot	LOD 95% (IU/mL)	95% CI (IU/mL)
WHO (Plasma)	1	3.3	2.4 - 4.2
	2	4.0	2.7 - 5.2
	3	4.0	2.8 - 5.2
WHO (Serum)	1	6.1	4.2 - 7.9
	2	2.6	1.9 - 3.3
	3	2.3	1.8 - 2.9

Hit rate analysis shows a positivity of > 95% at 6 IU/mL for the HCV genotype 1 material tested as shown in Table 3.

Table 3. HCV VL LOD for HCV Genotype 1 in EDTA Plasma and Serum

Specimen	Concentration (IU/mL)	No. Replicates	No. Positives	Positivity Rate (%)
WHO (Plasma)	0.5[a]	49	24	49
	1	72	47	65
	2	72	61	85
	3	72	69	96
	4	72	67	93
	6	72	71	99
	8	73	73	100
	10	72	72	100
WHO (Serum)	0.5[a]	53	21	40
	1	73	47	64
	2	73	64	88
	3	72	69	96
	4	73	71	97
	6	72	71	99
	8	72	70	97
	10	72	72	100

a. 0.5 IU/mL was added day 2 due to the high positivity rate observed at 1 IU/mL after day 1

In addition, dilutions of clinical specimens representing HCV genotype 1a, 2b, 3a, 4a, 5a and 6a in negative human EDTA plasma were analyzed with one reagent lot and 24 replicates per concentration level. The assignment of the nominal concentration of clinical specimens was determined by Abbott RealTime HCV™ assay. Hit rate analysis shows a positivity of >95% for all genotypes at 10 IU/mL as shown in Table 4.

Table 4. HCV VL LOD Hit Rate Analysis for HCV Genotype 1 – 6 Specimens in EDTA Plasma

Genotype	Lowest Concentration Level > 95% Hit Rate (IU/mL)	Hit Rate (%)
1a	10	100
2b	4	100
3a	6	100
4a	4	100
5a	2	96
6a	4	96

18.2 Limit of Quantitation

The total analytical error (TAE) was calculated using estimates determined through analysis of data from LOD study (WHO standard) and the Precision/Reproducibility study according to CLSI guideline E17-A2. The TAE for the dilutions that had an observed concentration at or near the assay limit of detection 10 IU/mL (1.0 $\log_{10}$) are presented in Table 5. TAE was estimated by two different methods.

Table 5. HCV VL TAE Analysis for Determination of LOQ

Specimen (Study)	DL Lot	N	Concentration (Log10 IU/mL)		Bias	Total SD	TAE[a] Absolute Bias + 2xSD	TAE[b] 2xSQRT (2)xSD
			Expected	Observed				
Acrometrix (Precision)	DL1	72	1.40	1.31	0.09	0.15	0.38	0.41
	DL2	72	1.40	1.29	0.11	0.14	0.40	0.41
	DL3	72	1.40	1.24	0.16	0.12	0.41	0.35
Acrometrix (Precision)	DL1	72	1.00	0.92	0.08	0.22	0.52	0.62
	DL2	72	1.00	0.82	0.18	0.18	0.54	0.51
	DL3	72	1.00	0.75	0.25	0.19	0.63	0.54
WHO, Plasma (LOD)	DL1	24	1.00	0.91	0.09	0.21	0.51	0.59
	DL2	24	1.00	0.82	0.18	0.30	0.78	0.86
	DL3	24	1.00	0.86	0.14	0.17	0.48	0.48
WHO, Serum (LOD)	DL1	24	1.00	0.96	0.04	0.13	0.30	0.37
	DL2	24	1.00	0.88	0.12	0.23	0.58	0.66
	DL3	24	1.00	0.80	0.20	0.18	0.57	0.52

a. TAE calculated according to the Westgard model in CLSI EP17-A2 (Section 6.2)
b. TAE based upon the difference between two measurements approach

The results of the TAE analysis demonstrate that the HCV VL assay can determine 10 IU/mL (1.0 $\log_{10}$) with an acceptable trueness and precision.

18.3 Precision/Reproducibility

The precision/reproducibility of the HCV VL assay was determined by analysis of parallel dilutions of HCV reference materials in HCV negative EDTA plasma. The nominal concentration of the reference material used was calibrated to the WHO 4th HCV International Standard (06/102). The study was a two site, blinded, comparative study using a seven-member panel of HCV reference material in HCV negative EDTA plasma with RNA concentrations that span the HCV VL assay quantitation range. Two operators at each of the two study sites tested one panel of twenty-one samples once per day over six testing days per lot. One site used an Infinity-80 instrument and the other site used GeneXpert Dx instruments. Three lots of HCV VL assay reagents were used for the study. Precision/reproducibility was evaluated in accordance with "Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline" CLSI document EP5-A2. The precision results for each regent lot are shown in Table 6.

Table 6. HCV VL Precision per Lot

Expected HCV RNA Concentration log_{10} IU/mL	Total Precision per Lot					
	Lot 1		Lot 2		Lot 3	
	SD	CV[a]	SD	CV[a]	SD	CV[a]
1.0	0.23	55.8%	0.18	44.2%	0.20	48.1%
1.4	0.15	35.1%	0.15	35.8%	0.13	29.6%
2.7	0.09	20.7%	0.09	20.6%	0.09	20.2%
4.2	0.07	16.4%	0.08	18.9%	0.07	15.3%
5.4	0.12	28.3%	0.09	19.9%	0.07	16.2%
6.9	0.13	31.8%	0.09	20.9%	0.07	17.0%
8.2	0.10	22.7%	0.10	23.7%	0.08	17.8%

a. "CV" is lognormal CV, as obtained using the formula:

$$\text{CV(of the lognormal dist)} = \sqrt{10^{\ln(10)*\sigma^2} - 1}$$

The reproducibility and precision of the HCV VL assay was evaluated by using nested ANOVA with terms for Site/Instrument, Lot, Day, Operator/Run and Within-Run. The standard deviation and the percentage of variability due to each component of the log_{10} HCV transformed concentrations were calculated, see Table 7.

Table 7. Standard Deviation and Contributable Percentage of Variability for Each Term and Total Precision

HCV RNA Concentration log_{10} IU/mL			Contribution to Total Variance SD (CV%)										Total Precision			
			Site/Inst		Lot		Day		Operator/ Run		Within-Run		Total			
Expected	Actual	N	SD	(%)[a]	SD	(%)[a]	SD	(%)[a]	SD	(%)[a]	SD	(%)[a]	SD	Lower CI	Upper CI	CV[b]
1.0	0.83	216	0.03	1.8%	0.08	13.2%	0.04	3.5%	0.00	0.0%	0.19	81.6%	0.21	0.18	0.25	51.7%
1.4	1.28	216	0.00	0.0%	0.04	7.1%	0.00	0.0%	0.00	0.0%	0.14	92.9%	0.14	0.13	0.16	34.1%
2.7	2.66	216	0.00	0.0%	0.04	17.2%	0.00	0.0%	0.02	3.2%	0.08	79.5%	0.09	0.08	0.11	22.1%
4.2	4.18	215	0.00	0.0%	0.05	30.9%	0.01	2.6%	0.00	0.0%	0.07	66.5%	0.09	0.07	0.12	20.6%
5.4	5.44	216	0.00	0.0%	0.06	26.5%	0.00	0.0%	0.01	1.3%	0.09	72.2%	0.11	0.09	0.14	25.8%
6.9	6.86	216	0.00	0.0%	0.07	34.0%	0.02	3.4%	0.00	0.0%	0.10	62.5%	0.13	0.10	0.17	29.8%
8.2	8.11	216	0.00	0.0%	0.09	47.9%	0.00	0.0%	0.02	2.6%	0.09	49.5%	0.13	0.10	0.19	30.5%

a. (%) is contribution of variance component to overall lognormal CV
b. “CV” is lognormal CV, as obtained using the formula:

$$CV(\text{of the lognormal dist}) = \sqrt{10^{\ln(10)*\sigma^2} - 1}$$

18.4 Linear Range and Inclusivity

The linear range of the HCV VL assay was determined by analysis of a twelve member panel covering a range from ~5 (0.75 $\log_{10}$) to ~1 x 10^8 (8 $\log_{10}$) IU/mL. Panels were prepared by parallel dilutions of HCV reference material (Armored RNA® genotype 1 and clinical specimen genotype 1) in HCV negative EDTA plasma and serum. The nominal concentration of the reference material used was calibrated to the WHO 4th HCV International Standard (06/102). Each panel member was tested in replicates of four on each of three testing days using two kit lots. Totally, 24 replicates per panel member and sample type were tested. The linearity analysis was performed according to CLSI guideline EP06-A. The combined results for both lots are shown in Figure 9 and Figure 10. The HCV VL assay is linear within a range 0.8–8.0 $\log_{10}$ IU/mL with a R^2 value of >0.997.

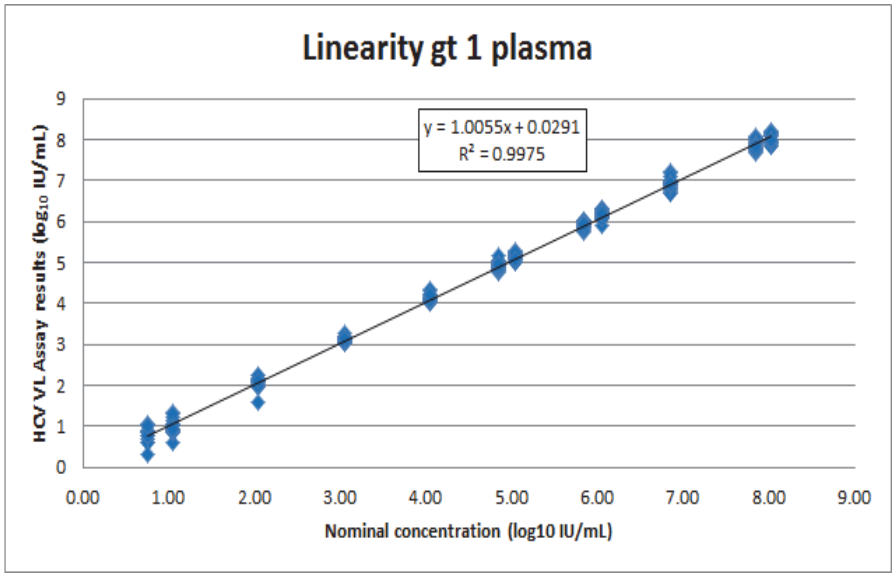


Figure 9. Linearity Genotype 1 in EDTA Plasma for the HCV VL Assay

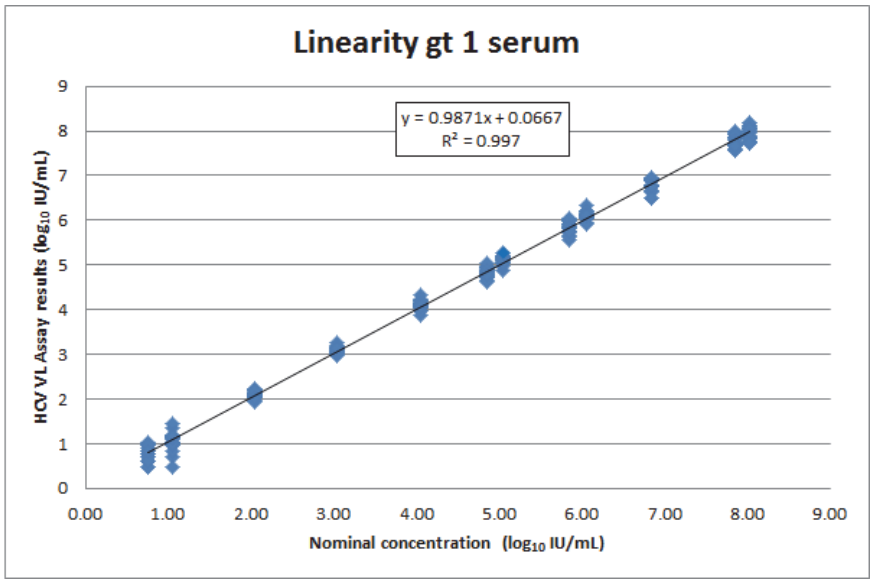


Figure 10. Linearity Genotype 1 in Serum for the HCV VL Assay

To confirm the linear range and evaluate the inclusivity of the HCV VL assay, panels consisting of clinical specimens representing HCV genotype 2 – 6 and Armored RNA® when available (genotypes 2 and 3 only) were prepared in negative human EDTA plasma. 7 – 13 panel members per genotype covering as wide a range as possible, varying from ~ 0.9 – 6 $\log_{10}$ IU/mL for genotype 5 to ~ 0.9 – 8.3 $\log_{10}$ for genotype 3, were prepared and analyzed in replicates of four on each of three testing days using two kit lots. For each genotype, 24 replicates per panel member were tested. The nominal concentrations of the reference materials used were calibrated to the WHO 4th HCV International Standard (06/102). All genotypes responded linearly with R^2 values ranging from 0.994 – 0.998.

18.5 Analytical Specificity (Exclusivity)

The analytical specificity of the HCV VL assay was evaluated by adding potentially cross-reacting organisms at 1 x 10^5 CFU/mL, copies/mL or $TCID_{50}$/mL input concentration into HCV negative EDTA plasma and in plasma that contained ~25 IU/mL HCV reference material (clinical specimen genotype 1). Tested organisms are listed in Table 8.

Table 8. Analytical Specificity Organisms

Human Immunodeficiency virus 1
Human Immunodeficiency virus 2
Human T-cell lymphotropic virus I
Human T-cell lymphotropic virus II
Candida albicans
Cytomegalovirus
Epstein-Barr virus
Hepatitis A virus
Hepatitis B virus
Herpes simplex virus 1
Herpes simplex virus 2
Human herpes virus 6
Human herpes virus 8
Varicella Zoster virus
BK Human polyoma virus
Banzi virus
Ilheus virus
West Nile virus
Zika virus
Human papilloma virus 16
Human papilloma virus 18
Staphylococcus epidermidis
Staphylococcus aureus

None of the tested organisms showed cross reactivity and all positive replicates resulted in concentrations of HCV RNA within ± 0.5 log from a HCV positive control when tested using the HCV VL assay. In addition to the species listed in Table 8, Dengue virus and vaccinia virus were analyzed *in silico* since material representing the viruses could not be obtained for testing. No practical significant sequence similarity was found between the analyzed viruses and the primers and probes of the Xpert HCV VL assay.

18.6 Potentially Interfering Substances

The susceptibility of the HCV VL assay to interference by elevated levels of endogenous substances, by drugs prescribed to HCV infected patients and by autoimmune disease markers was evaluated. HCV negative EDTA plasma and plasma that contained ~25 IU/mL HCV reference material (clinical specimen genotype 1) were tested.

Elevated levels of the endogenous substances listed in Table 9 were shown not to interfere with the quantification of the HCV VL assay or impact the assay specificity.

Table 9. Endogenous Substances and Concentration Tested

Substance	Tested Concentration
Albumin	9 g/dL
Bilirubin	20 mg/dL
Hemoglobin	500 mg/dL
Human DNA	0.4 mg/dL
Triglycerides	3000 mg/dL

The drug components as presented in Table 10 were shown not to interfere with the quantification of the HCV VL assay or impact the assay specificity when tested at three times peak level concentration in five drug pools.

Table 10. Drug Pools Tested

Pool	Drugs
Control	N/A
1	Zidovudine, Saquinavir, Ritonavir, Interferon alfa-2b, Clarithromycin
2	Abacavir sulfate, Fosamperavir Calcium, Peginterferon 2b, Ribavirin
3	Tenofovir disoproxil fumarate, Lamivudine (3TC), Indinavir sulfate, Ganciclovir, Valganciclovir HCl, Acyclovir
4	Stavudine (d4T), Efavirenz, Lopinavir, Enfuvirtide (T-20), Ciprofloxacin
5	Nevirapine, Nelfinavir mesylate, Azithromycin, Valacyclovir HCl

Testing of specimens from ten individuals per autoimmune disease marker shows no interference with the autoimmune disease markers systemic lupus erythematosus (SLE), anti-nuclear antibody (ANA), or rheumatoid factor (RF) using the HCV VL assay.

18.7 Sample Collection Media Equivalence (EDTA, PPT-EDTA and Serum)

For each sample collection media (EDTA, PPT-EDTA and serum) specimens from 50 matched HCV positive individuals and 25 matched HCV negative specimens were collected and tested using one kit lot of the HCV VL assay.

As shown in Figure 11 and Figure 12 equivalent performance of the HCV VL assay was shown for EDTA plasma versus serum samples and EDTA plasma versus PPT-EDTA plasma samples. All HCV positive specimens collected in serum or PPT-EDTA plasma produced concentrations of HCV RNA within ±0.5 $\log_{10}$ IU/mL of the HCV positive specimen collected in EDTA plasma when tested using the HCV VL assay.

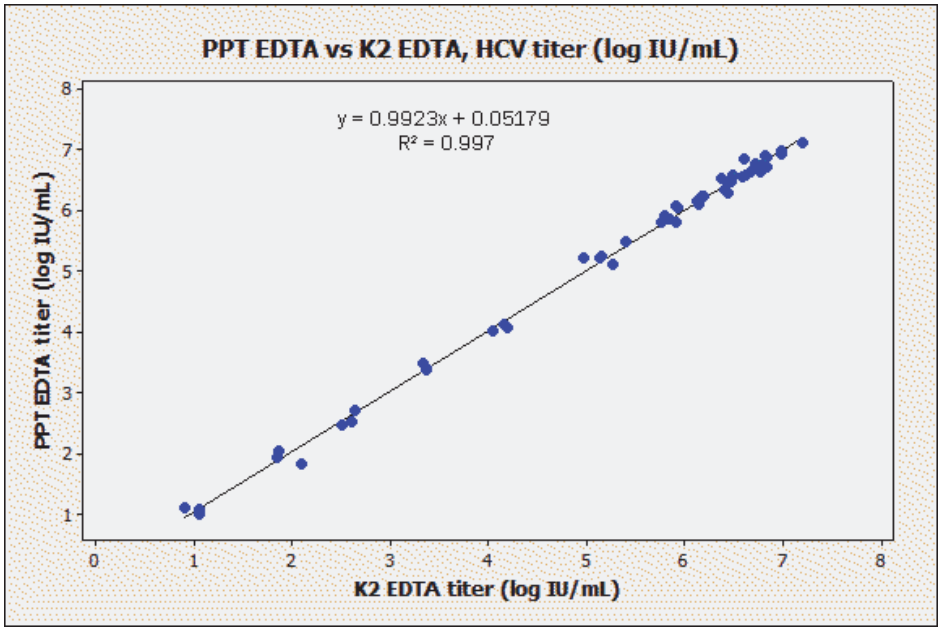


Figure 11. Scatterplot of Log IU/mL PPT-EDTA versus Log IU/mL EDTA

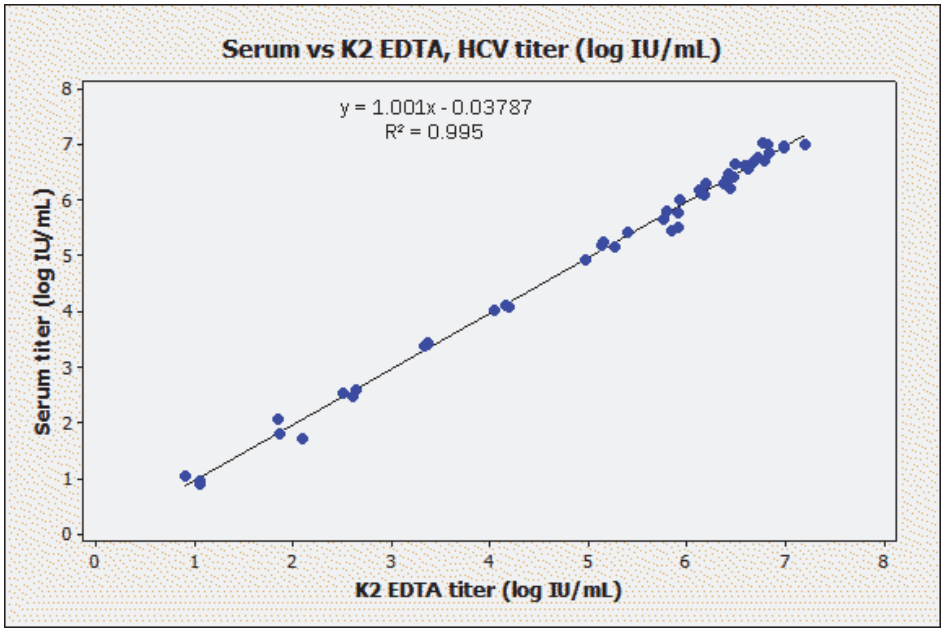


Figure 12. Scatterplot of Log IU/mL Serum versus Log IU/mL EDTA Plasma

19 Performance Characteristics – Clinical Performance

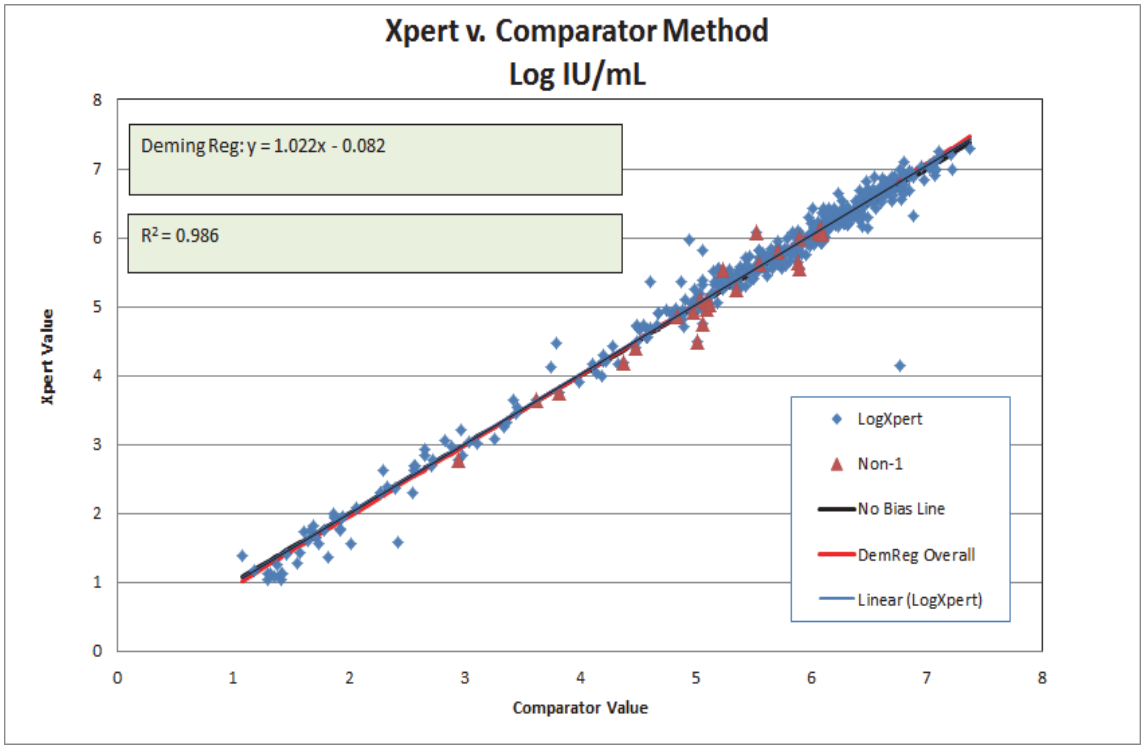
Specificity

The specificity of the HCV VL assay was evaluated using 100 EDTA plasma specimens from HCV negative blood donors. None of the 100 specimens tested were detected by the HCV VL assay equating to 100% specificity (95% CI = 96.1-100).

Method Correlation

A multi-site study was conducted to evaluate the performance of the HCV VL assay relative to a comparator method using fresh and frozen human plasma or serum specimens collected from HCV infected individuals. Of the 607 eligible specimens, each from unique individuals, 408 (67.2%) were collected from male subjects. The average age was 50.2 ± 13.2 years with an age range of 21 to 86 years.

Of the 607 specimens, 389 were within the quantitation range of both assays including 23 specimens that were HCV non-1 genotypes (2, 2a, 2b, 2c, 3, 3a, 4 & 6) and one mixed genotype (HCV 1 & 6). The Deming regression shows very good correlation between the HCV VL and the comparator method with a slope of 1.022 and intercept of 0.082. The R^2 was 0.986.



*HCV non-1 genotypes are represented as triangles. A single outlier was not included in the analysis.

Figure 13. Xpert v. Comparator Method

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12. Occupational Safety and Health Standards, Hazard Communication, Toxic and Hazard Substances (March 26, 2012) (29 C.F.R., pt. 1910, subpt. Z).

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- Lot number
- Serial number of the instrument
- Error messages (if any)
- Software version and, if applicable, Computer Service Tag number

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23 Table of Symbols

Symbol	Meaning
REF	Catalog number
IVD	*In vitro* diagnostic medical device
	Do not reuse
LOT	Batch code
	Caution
	Manufacturer
	Contains sufficient for <n> tests
CONTROL	Control
	Expiration date
CE	CE marking – European Conformity
	Temperature limitation
	Biological risks
	Warning

Cepheid AB
Röntgenvägen 5
SE-171 54 Solna
Sweden

CE 2797 IVD

GeneXpert®
Powered By CEPHEID INNOVATION

Xpert® Check Instructions for Use

REF **XPERTCHECK-CE-5**

Cepheid®

In Vitro Diagnostic Medical Device IVD CE

302-6125, Rev. A August 2022

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See Revision History for a description of changes.

Revision History

Description of changes: 301-3985, Rev. J to 302-6125, Rev A

Purpose: To align with the requirements of Regulation (EU) 2017/746

Section	Description of Change
Front Section	Updated Copyright Information
Preface	Added EU/Switzerland Importer Information
Preface	Added CH REP symbol to Table of Symbols
1.3	Revised Intended Use section structure and added Intended Usage/Environment.
1.5.1	Added new Note regarding bovine serum albumin in the beads.
1.7	Corrected typo. Changed “DX” to Dx” in 2 places.

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Preface

About This Document

The *Xpert Check Package Insert* provides instructions on running Xpert Check software for checking module performance.

Safety Information

Read and understand any safety information presented in this document before you begin operating the instrument. Make sure you follow the precautionary statements presented in this guide:

Caution 	**Indicates that damage to the system, loss of data, or invalid results could occur if the user fails to comply with the advice given.**
Important	**Highlights information that is critical for the completion of a task or the optimal performance of the system.**
Note	Identifies information that applies only in special cases.

Related Documents

For other information outside the scope of this document, see the following publications:

- *GeneXpert Dx Operator Manual*
- *GeneXpert Xpress User's Guide*
- *GeneXpert Infinity Operator Manual*

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- Error messages (if any)
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Table of Symbols

Symbol	Meaning
	Catalog number
	*In vitro* diagnostic medical device
	Batch code
	Do not reuse
	This type of symbol indicates a Warning or Caution for which there is no other identified symbol. Read the instructions following the symbol to avoid injury or equipment damage.
	Consult instructions for use
	Manufacturer
	Country of manufacture
	Contains sufficient for <n> tests
	Expiration date
	Control
	CE marking - European Conformity
	Authorized representative in the European Community
	Authorized representative in Switzerland
	Temperature limitation
	This type of warning label indicates a potential biological hazard risk. Biological samples such as tissues, body fluids, and blood of humans and/or animals have the potential to transmit infectious diseases. Follow your local, state/ provincial, and national safety regulations for handling and disposing the samples.

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Table of Contents

List of Figures

1 Introduction

Important **Read and understand this entire document before performing the data collection procedure.**

1.1 Proprietary Name

Xpert® Check

1.2 Common or Usual Name

Xpert Check

1.3 Intended Purpose

1.3.1 Intended Use

Xpert® Check is part of a check, verification, and hardware test system for GeneXpert® modules. Xpert Check is used in GeneXpert Dx, GeneXpert Xpress and GeneXpert Infinity systems. Xpert Check is used to check the optical system, verify the thermal system and perform a series of system-level tests to ensure full system functionality within Cepheid's instrument servicing specifications. One Xpert Check cartridge is usually used to check a single module in conjunction with the Xpert Check software. In certain cases where a retest is required, multiple cartridges may be necessary to test a module.

1.3.2 Intended User/Environment

Xpert® Check is intended to be performed by trained users where a GeneXpert System is installed.

1.4 Summary and Explanation

The GeneXpert module is the basis for all GeneXpert instrument systems worldwide. Cepheid recommends that the system be checked for proper operation on an annual basis. Based upon the usage and care of each system, checks may be recommended more frequently. The system is designed to detect module issues with the internal assay controls.

Xpert Check is an accessory to GeneXpert systems. Xpert Check includes reagents for the optical checking and performance verification of the module. Probe Check Controls (PCCs) verify reagent rehydration, PCR tube filling in the cartridge, probe integrity, and reagent stability. Thermal performance is verified via proprietary thermal probe chemistries, and module hardware performance is tested and verified by a suite of subsystem-specific tests which exercise all critical elements of the GX module.

The Xpert Check process consists of two phases. The first phase is the execution of module testing using the cartridges. The second phase consists of a Cepheid Quality Assurance Review, followed by the issuance of an Xpert Check code to complete the Xpert Check process. **The Xpert Check process is not complete until this code is applied to the system**.

1.5 Reagents and Instruments

1.5.1 Materials Provided

The Xpert Check kit contains the following:

Table 1-1. Kit Contents

Description	Quantity
Xpert Check cartridges with integrated reaction tubes	**5 per kit**
Each cartridge contains the following materials:	
• Bead 1	**1 per cartridge**
• Reagent 1	**1.0 mL per cartridge**
I-CORE Lens Cleaning Brush	**4 per kit**
PI/Software (P/N 950-0413)	**1 per kit**
Data CD	**1 per kit**

Note Safety Data Sheets (SDS) are available at www.cepheidinternational.com under the **SUPPORT** tab.

Note The bovine serum albumin (BSA) in the beads within this product was produced and manufactured exclusively from bovine plasma sourced in the United States. No ruminant protein or other animal protein was fed to the animals; the animals passed ante- and postmortem testing. During processing, there was no commingling of the material with other animal materials.

1.5.2 Storage and Handling

- Store the Xpert Check cartridges at 2-28 °C. Wait at least 10 minutes after removal from cold storage before using, to allow a cartridge to reach ambient temperature.
- Use the cartridge within 48 hours of opening the foil pouch.
- Discard cartridges that have been removed from their foil-wrapped pouches outside of the approved usage interval.

- Do not use cartridges that have passed the expiration date.
- Do not open a cartridge lid until you are ready to perform testing.
- The cartridge lid must be opened (vented) prior to use of the cartridge; however, no sample is required for testing.
- Discard all used and unused materials, including cleaning brushes and cartridges once the Xpert Check session is completed.

Note Contents of cartridges are non-hazardous.

1.5.3 Materials Required but Not Provided

- GeneXpert Dx, GeneXpert Xpress or GeneXpert Infinity System with Cepheid-supplied computer and barcode scanner.
- GeneXpert instrument.

1.6 Limitations

- For use with GeneXpert modules (running GeneXpert Dx software version 4.0 and above or GeneXpert Xpress software version 6.2 and above). 4-color GeneXpert modules (including Bio-threat modules) and Dual-Cal modules cannot run Xpert Check and must be tested by Cepheid Service.
- Use of the Xpert Check kit does not guarantee that the GeneXpert instrument will be free of hardware failures, nor does it take the place of a Cepheid Service Agreement.

1.7 Warnings and Precautions

Important

After January 14, 2020, Microsoft will no longer provide security updates or support for PCs running Windows 7. It is recommended that you upgrade to Windows 10.

Please contact: https://www.microsoft.com/en-us/microsoft-365/windows/end-of-windows-7-support for Windows 7 support information.

In addition, please contact your local Cepheid Technical Support if you have questions about using Windows 7.

- Even though Xpert Check cartridges do not contain hazardous chemicals, you should always follow your institution’s safety procedures for working with chemicals.
- Do not add a sample or other reagents to the Xpert Check cartridges.
- Do not use a cartridge that has a damaged reaction tube.
- Do not use cartridges from visibly damaged or compromised foil pouches.

- Contact your local Cepheid Technical Support office for replacement of damaged kit contents.
- Do not use a cartridge if it is dropped.
- ② Each single-use Xpert Check cartridge is used to process one test. Do not reuse spent cartridges.
- Each cleaning brush is intended for use in a single module. Do not re-use brushes in multiple modules.
- Do not open a cartridge package or break the lid seal until you are ready to perform testing.
- Allow the Xpert Check cartridge to come to ambient temperature prior to use if it has been placed in cold storage. Wait at least 10 minutes after removal from cold storage before using.
- Do not store single cartridges. Cartridges left over from an Xpert Check session, including pouched/unopened cartridges should be discarded along with spent cartridges.
- Do not use cartridges whose shelf life has expired. The system will detect expired cartridges and abort the test.
- Follow your institution’s environmental waste procedures/consult your institution's environmental waste personnel for proper disposal of cartridges. If necessary, reference the WHO's [World Health Organization's] waste handling and disposal guidelines for the proper disposal of cartridges.
- Once a cartridge barcode has been scanned, do not substitute another cartridge in place of the scanned cartridge.
- If using an internet-enabled Xpert Check, it is recommended that up-to-date anti-virus software be installed on the desktop or laptop computer with updated virus definition files, prior to executing Xpert Check.
- Prior to running Xpert Check, ensure that the environmental operating temperature is within the correct limits (15 °C–30 °C). Xpert Check will render a system’s modules unavailable if the internal temperature is above 40 °C. The internal temperature can be verified in the Maintenance section of the GeneXpert Dx, GeneXpert Infinity or GeneXpert Xpress software. Do not proceed under these conditions.
- Xpert Check expects the same computer to be used throughout the entire process. The computer installed with the GeneXpert system should be used, and not another computer from a different GeneXpert system.
- The Xpert Check code will expire if not applied within 45 days of completion of running Xpert Check.

1.8 Chemical Hazards

According to the Globally Harmonized System for Classification and Labeling (GHS) and the Classification, Labeling and Packaging (CLP) Regulation, this material is not considered hazardous.

1.9 Assistance and Contact Information

For a complete listing of Cepheid technical support, service support, sales support, and headquarters contacts, please see Technical Assistance, in the Preface of this document.

1.10 Software Buttons, Icons and Symbols

Table 1-2. Software Buttons, Icons and Symbols

Symbol	Definition
	**Information.** Touch or click this icon to obtain additional information. Displays the Information Key workspace screen which has an explanation of the various module icon displays.
	**Continue**. This icon is located at the bottom of most screens. Touch or Click this icon to advance the display to the next screen.
	**Continue to End.** Touching or clicking this icon moves the user to the last screen.
	**Exit**. Exits the Xpert Check application.
	**About**. Brings up the About screen which shows the name of the software, the software version number, copyright notice, etc.
	**Home**. Go to the Home screen.

Table 1-2. Software Buttons, Icons and Symbols

Symbol	Definition
	**Repeat/Retry**. Retry loading an Xpert check cartridge to attempt to check a module that has had an unsuccessful test of a minor nature or if the cartridge has not been vented by the user. Used on the 'Check Test' screen.
	**Back.** Touching or clicking this icon takes the user to the previous screen.
	**Cancel.** Cancel the current operation. In most cases this will mean going back to the previous screen. In some cases, it may mean going back to the screen before the one that started the current operation.
	**Select none of the modules for check.** Deselects all modules for checking. If you only want to check a few modules, you may deselect ALL of them, and then reselect only the ones you wish to check.
	**Select all of the modules for checking**. The default setting for the system.
	**Connectivity Status.** Indicates the system is able to reach the Xpert Connectivity Center.
	**Connectivity Status.** Indicates the system is not able to reach the Xpert Connectivity Center.
	**Module unsupported for Xpert Check.** Skip the current module and do NOT attempt to check the current module.
	Module selected for Xpert Check. Module will be included when Xpert Check is run.

Table 1-2. Software Buttons, Icons and Symbols

Symbol	Definition
	**Skip Current Module.** Skip the current module and do not attempt to Xpert Check the current module. Used on the 'Load Xpert Check Cartridges' screen.
	**Skip Remaining Modules.** Skip all the remaining modules and do NOT attempt to Xpert Check them. Used on the 'Load Xpert Check Cartridges' screen.
	Module not selected for Xpert Check. Module will not be included when Xpert Check is run.
	**Module unavailable for Xpert Check.** Module will not be included when Xpert Check is run.
	Indicates a module with data collection in progress.
	Indicates data collection complete.
	**Retest required. I**ndicates an incomplete Xpert Check data collection. A message will notify the user that the test must be rerun. A further message will indicate if the existing cartridge can be reused for the test or if a new cartridge must be used.

Table 1-2. Software Buttons, Icons and Symbols

Symbol	Definition
	**Service required.** Contact the Cepheid Authorized Service Provider (ASP) or your local Cepheid Technical Support office.
	**Lost communication.** Contact the Cepheid Authorized Service Provider (ASP) or your local Cepheid Technical Support office.
	**Burn.** Burn a CD containing the collected Xpert check information (for users without an active internet connection).
	**Collect Xpert Check Data.** Leads the user through the Xpert Check data collection process.
	**Enter Xpert Check code.** Go to the 'Enter Xpert Check Code' screen.
	**Xpert Check Status.** Go to the Xpert Check Status screen to review Xpert Check status.
	**Upload Xpert Check Data File.** Go to the 'Upload Xpert Check Code Data File' screen.
	**Upload Xpert Check Data CD.** Go to the 'Upload Xpert Check Code Data CD' screen.
	**Write Xpert Check Code.** Write an Xpert Check Code to a file.
	**Read Xpert Check Code.** Open a file to read the Xpert Check code.
	**Scan.** Turn the barcode scanner on, and accept the next scanned input.

Table 1-2. Software Buttons, Icons and Symbols

Symbol	Definition
	**View and Print.** Launch the Adobe Reader so you can view and then print a PDF file.

2 Procedure

2.1 System Preparation

Note Prepare the system for Xpert Check by following one of the four procedures listed in this section for the GeneXpert Dx, GeneXpert Xpress, the GeneXpert Infinity-48s, or the GeneXpert Infinity-80.

Important **Authorized Service Providers (ASPs) who perform Xpert Check but won't be on-site when the Xpert Check code numbers come back (non-internet connection sites), should leave the user name and password for the users to log in later to enter the codes (see section 2.3.2).**

2.1.1 GeneXpert Dx Preparation

1. Create an Administrator or Basic level User Name and Password in the GeneXpert software if one does not exist. Xpert Check requires this logon credential to be established prior to starting.
2. Have your Authorized Service Provider (ASP) code available before continuing to the next steps.
3. Exit the GeneXpert Dx software.
4. Go to Section 2.2, GeneXpert Dx, GeneXpert Xpress and GeneXpert Infinity Optics Cleaning.

2.1.2 GeneXpert Xpress Preparation

1. Create an Administrator or Basic level User Name and Password in the GeneXpert Xpress software if one does not exist. Xpert Check requires this logon credential to be established prior to starting.
2. Have your Authorized Service Provider (ASP) code available before continuing to the next steps.
3. Exit the GeneXpert Xpress software.
4. Go to Section 2.2, GeneXpert Dx, GeneXpert Xpress and GeneXpert Infinity Optics Cleaning.

2.1.3 GeneXpert Infinity-48s or GeneXpert Infinity-80 Preparation

1. Create an Administrator or Basic level User Name and Password in the GeneXpert software if one does not exist. Xpert Check requires this logon credential to be established prior to starting.

2. Have your Authorized Service Provider (ASP) code available before continuing to the next steps.
3. Exit the GeneXpert Infinity System software.
4. Open the glass doors following the instructions in the *GeneXpert Infinity System Operator Manual*.
5. Go to Section 2.2, GeneXpert Dx, GeneXpert Xpress and GeneXpert Infinity Optics Cleaning.

2.2 GeneXpert Dx, GeneXpert Xpress and GeneXpert Infinity Optics Cleaning

This procedure describes the method for removing dust and tube debris from the surface of rod lenses of the excite and detect blocks for GeneXpert Dx, GeneXpert Xpress and GeneXpert Infinity modules prior to performing the Xpert Check procedure.

Materials Required or Recommended for Cleaning

- I-CORE Lens Cleaning brush (Quantity of four Included in the Xpert Check kit)
- Disposable gloves

Estimated Cleaning Time: 30 Seconds per module.

2.2.1 I-CORE Lens Cleaning Procedure

1. Select the module to be checked and manually open the door of the module.
2. If necessary, remove the cartridge from the module.

Biological Risks

Remove the cartridge from the GeneXpert modules prior to cleaning. Failure to remove a cartridge could result in personnel being exposed to biological hazards and/or liquid biological materials spilling into the instrument and causing damage to the instrument.

3. Locate the brush provided in the Xpert Check kit (see Figure 2-1).

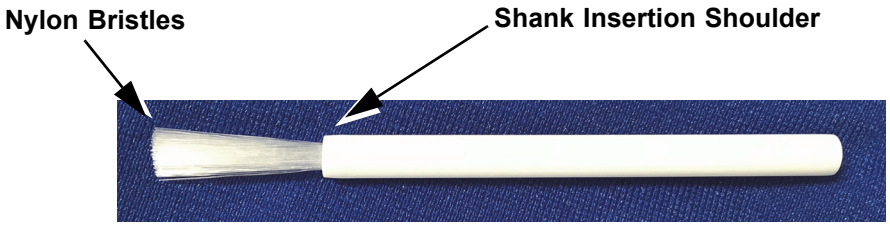


Figure 2-1. I-CORE Lens Cleaning Brush

Note

The brush is designed so that it will easily insert into the I-CORE slit and make contact with the rod lenses of the excite and detect blocks.

Biological Risks

Make sure you wear disposable gloves for the cleaning process. Wearing gloves prevents you from being exposed to biologically hazardous materials.

4. Wearing disposable gloves, insert the brush into the I-CORE slit in a tilted manner up to the shank insertion shoulder, as shown in Figure 2-2.

Note

Make sure that all the bristles are fully inserted (up to the shoulder of the plastic shank of the brush) so that it does not cause unnecessary damage to the brush.

Caution

Do not insert any objects into the I-CORE slit except the provided brush. Inserting any other object may damage the I-CORE.

Caution

Do not apply any solution (such as ethanol or bleach) onto the brush bristles. The brush must be completely dry when inserting it into the I-CORE slit.

Important

The brush is intended for single-use and should not be used on more than one module. Use a new brush for each module to be cleaned.

Figure 2-2. Inserting the Cleaning Brush into the I-CORE Slit

5. Insert the brush into the I-CORE slit completely up to the plastic shank (shoulder) of the brush. Hold the brush firmly in the I-CORE slit, and perform cleaning of the rod lenses as described below. The entire cleaning process should take approximately 30 seconds per module.

Note

Cleaning is done by moving the brush in an up and down direction within the I-CORE slit. Brush rotation, even if it has to be done, is not the main action that results in optics cleaning.

A. Begin by brushing from the top of the I-CORE slit to the bottom, making sure to apply a uniform pressure when brushing from the top to the bottom of the I-CORE slit. This will ensure that most of the tube debris and dust is brushed off from the surface of the lenses.

B. Rotate the brush from left to right and back again, approximately 180°.

C. Brush once more from the top of the I-CORE slit to the bottom.

D. Rotate the brush again from left to right and back again, approximately 180°.

E. Finally, brush again from the top of the I-CORE slit to the bottom.

6. When lens cleaning is complete, remove and discard the used brush and gloves as hazardous waste.

Important

Dispose of gloves and brushes according to your institution's safety policies and procedures for hazardous waste.

7. Proceed to Section 2.3, Data Collection Procedure: GeneXpert Dx, GeneXpert Xpress and GeneXpert Infinity.

2.3 Data Collection Procedure: GeneXpert Dx, GeneXpert Xpress and GeneXpert Infinity

Important

Before collecting data, be sure to prepare the system for checking as described in Section 2.1, System Preparation.
Internet-connected users should verify their system's connectivity status prior to beginning the Xpert Check process.

Note

Throughout this procedure, when making an onscreen button or icon selection, use the touchscreen on the GeneXpert Xpress system by touching the button or icon with your finger. When using the GeneXpert Dx or GeneXpert Infinity system, use a mouse to select, by clicking the desired button or icon.

Note

Use care in inserting CD1 into the DVD drive. Be sure the CD is fully seated in the tray before closing the drive door.

1. Place Software CD1 in the computer connected to the GeneXpert Dx. For the GeneXpert Dx system using an external DVD drive and for the GeneXpert Xpress and GeneXpert Infinity systems, connect the DVD drive following the instructions in the *GeneXpert Dx Operator Manual*, the *GeneXpert Xpress User's Guide* or the *GeneXpert Infinity System Operator Manual*, and insert the CD into the DVD drive.

2. For a GeneXpert Xpress system, follow the procedure in Step A; for GeneXpert Dx and GeneXpert Infinity, follow the procedure in Step B.

   A. **GeneXpert Xpress** On the computer desktop, touch and hold the **Computer** icon and a drop-down menu will appear. Touch **Open**, then touch and hold the applicable drive letter for your DVD drive.
   Touch **Open** from the drop-down menu, and the files located on the CD will then be displayed.
   Find, touch and hold the **XpertCheck.exe** application, and when the drop-down menu appears, touch **Run** to install as administrator. When the software has been installed, a "wrench" icon will appear on the desktop.

Note The software may take some time to load from the CD.

   B. **GeneXpert Dx and GeneXpert Infinity:** On the computer desktop, right-click the **Computer** icon and a drop-down menu will appear. Click **Open**, then right-click on the applicable drive letter for your DVD drive.
   Select **Open** from the drop-down menu, and the files located on the CD will then be displayed.
   Find and right-click the **XpertCheck.exe** application, and when the drop-down menu appears, click **Run** to install as Administrator. When the software has been installed, a "wrench" icon will appear on the desktop.

Note The software may take some time to load from the CD.

3. Depending on your system, either touch or double-click the "wrench" icon to launch the Xpert Check program.

4. The Terms of Service screen appears first. Use the scroll bar to read through the entire document. You will be asked to select (touch or click) the check box (bottom of the screen) to verify that you have read and agree to the Terms of Service before continuing. See Figure 2-3.

Note The Xpert Check software runs on Windows 7 or Windows 10. The screens shown in this manual are from Xpert Check software running on Windows 7. Screens for Xpert Check software running on Windows 10 will be similar.

Important

After January 14, 2020, Microsoft will no longer provide security updates or support for PCs running Windows 7. It is recommended that you upgrade to Windows 10.

Please contact: https://www.microsoft.com/en-us/microsoft-365/windows/end-of-windows-7-support for Windows 7 support information.

In addition, please contact your local Cepheid Technical Support if you have questions about using Windows 7.

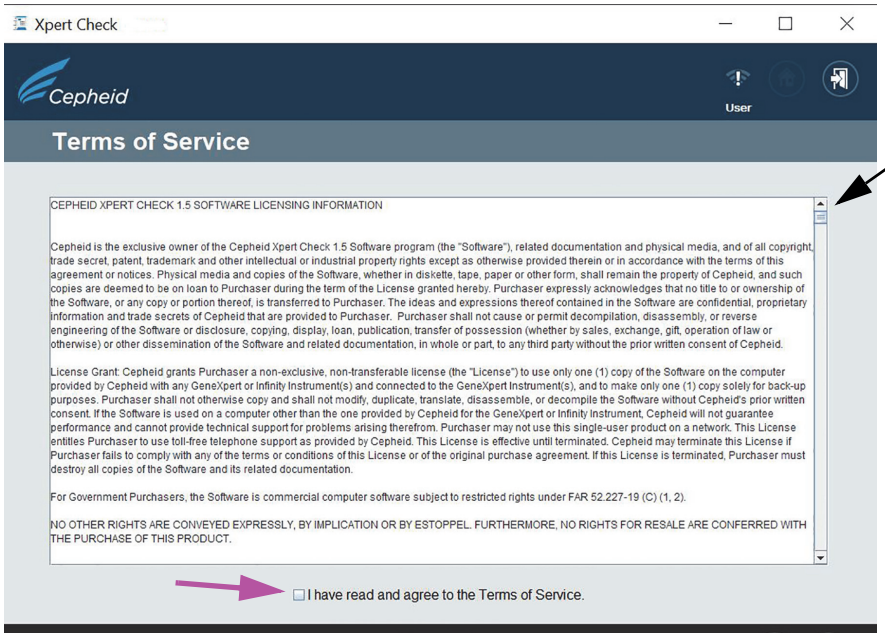


Figure 2-3. Terms of Service Screen

5. After agreeing to the Terms of Service, the Login screen will appear. Log in with your GeneXpert Dx, GeneXpert Xpress or GeneXpert Infinity designated Administrator level **USER NAME** and **PASSWORD** (previously assigned to you by your system administrator). After entering your login information, touch or click the forward arrow button at the bottom of the screen to advance to the Xpert Check Home screen. See Figure 2-4.

Note

On the GeneXpert Xpress system, touching any field for inputting usernames, passwords, text, etc., will cause a virtual keyboard to appear for data entry. To close the keyboard, touch the **X** key in the upper right corner of the keyboard.

Note

The user name and password are the same ones you used for the GeneXpert Dx, GeneXpert Xpress or GeneXpert Xpertise software.

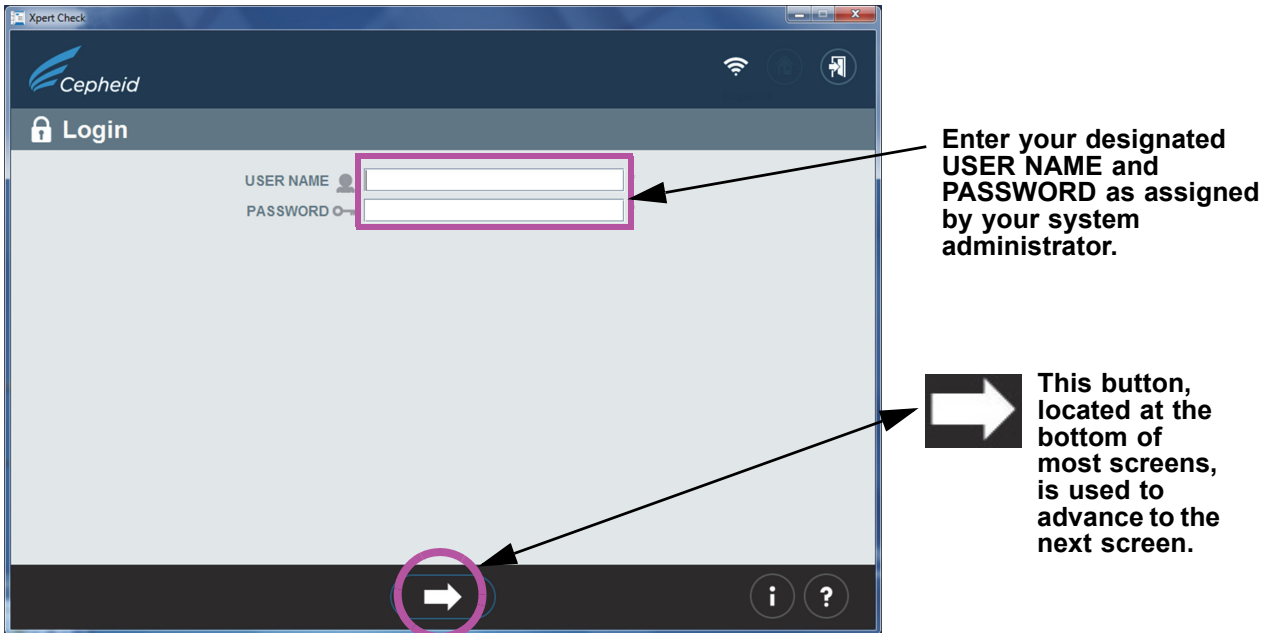


Figure 2-4. Xpert Check Login Screen

In case of a login error, the following screen will appear. See Figure 2-5.

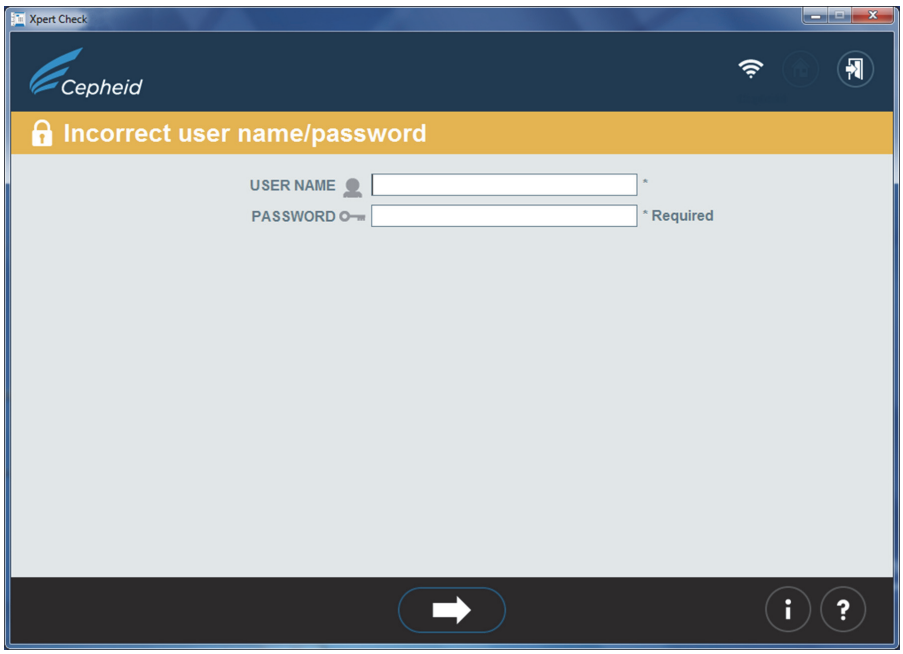


Figure 2-5. Login Error Screen

6. If a login error occurs, examine the **USER NAME** and **PASSWORD** entries for errors. If necessary, reenter the information and retry. After entering your login information, touch or click the forward arrow button at the bottom of the screen to advance to the Xpert Check Home screen.
7. Obtain a sufficient number of cartridges for the number of modules to be tested.

Important **Do not open cartridge packages until you are ready to scan the cartridge barcode (in Step 17).**

Note When determining the number of cartridges that will be needed for this test, the user should be aware of the number of modules that they will be checking.

8. Touch or click the **Collect Xpert Check Data** icon on the Home screen (See Figure 2-6). After a few seconds, the first Contact Information screen (Figure 2-7) will appear.

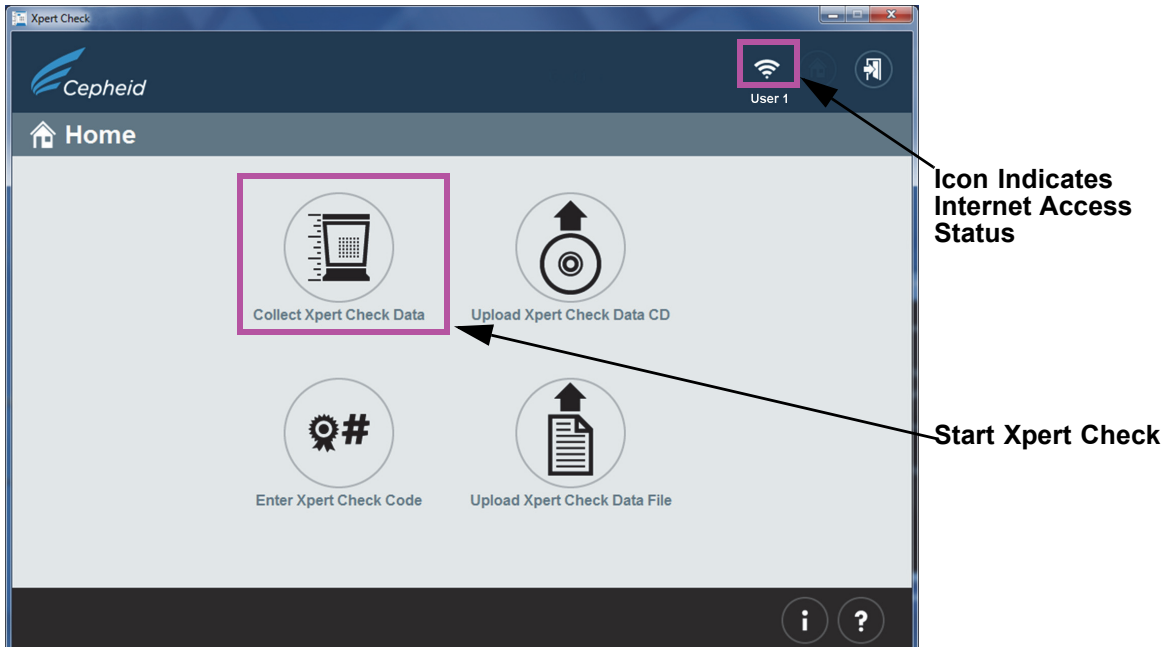


Figure 2-6. Home Screen

9. When the first of two Contact Information screens appear (see Figure 2-7 and Figure 2-8), fill out the fields in the two screens. Use the large navigation arrows at the bottom of the screens to move between the two screens.

Note GeneXpert Xpress: When you touch a field, an onscreen keyboard appears for entering data.

Note that fields marked with "*" (at the right of the entry area) are mandatory fields.

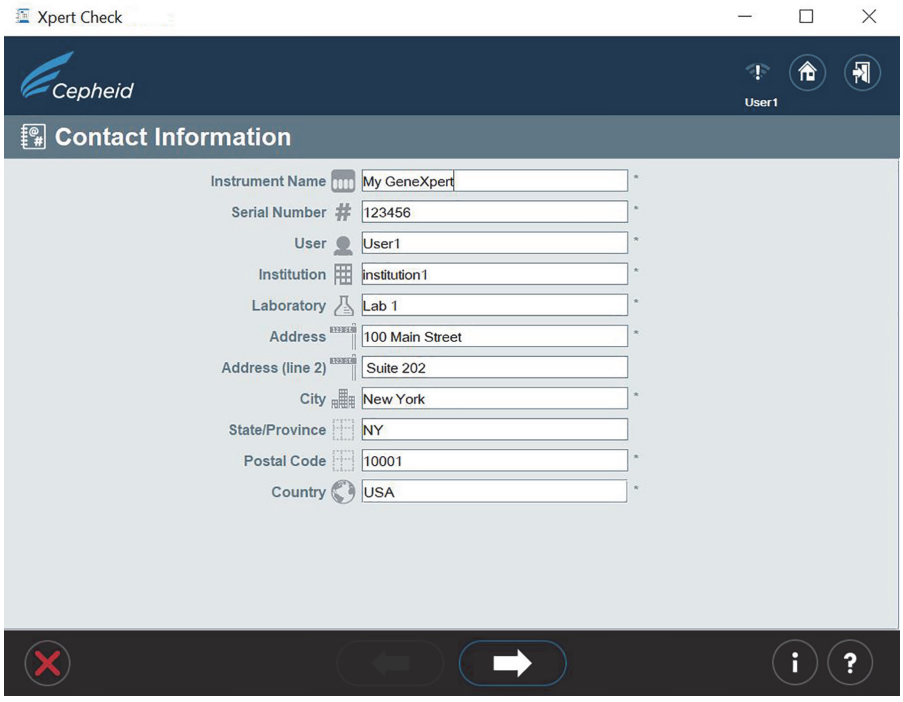
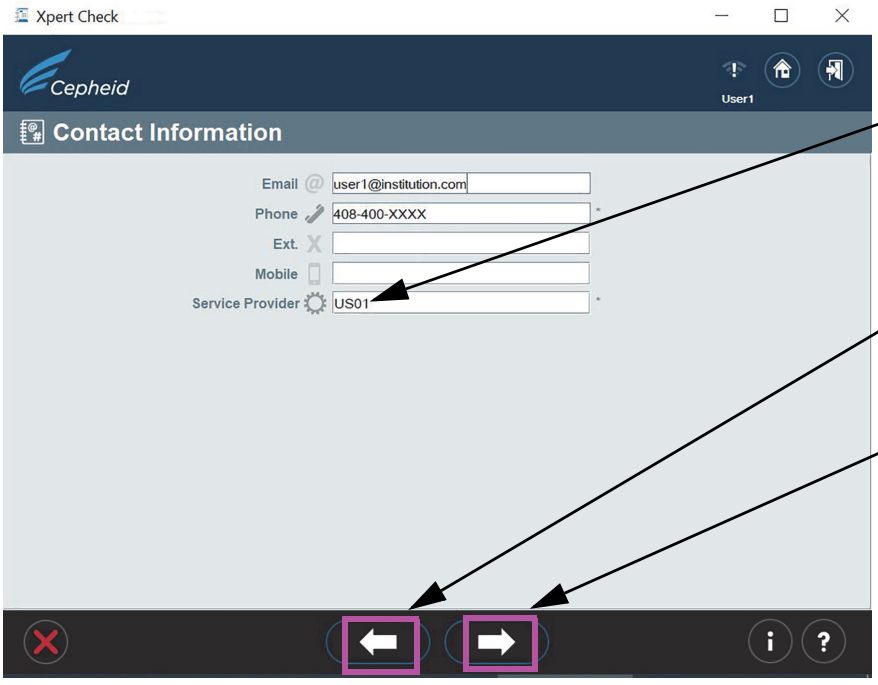


Figure 2-7. Contact Information Screen - Page 1



In this mandatory field, enter your Authorized Service Provider's ID code. The ID code is four characters, as described in the note below.

Clicking on this icon will take the user back to the first Contact Information screen

Clicking on this icon will take the user to the Open Module Doors screen

Figure 2-8. Contact Information Screen - Page 2

Note

The ASP-provided ID code for the Service Provider on the Contact Information screen consists of four characters. (As examples: US01, 1203, etc.)

10. When all information has been entered, touch or click the forward arrow button at the bottom of page 2 of the Contact Information screen. The Open Module Doors screen will appear. See Figure 2-9. Manually open all module doors to enable cartridge loading.

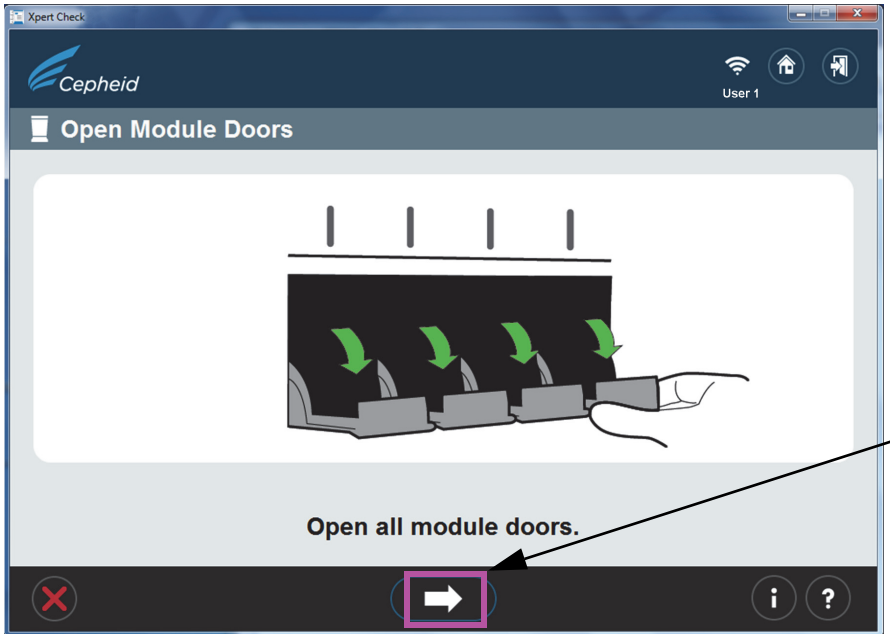


Figure 2-9. Open Module Doors Screen

11. After opening all the module doors, touch or click the forward arrow button at the bottom of the screen. The Module preparation screen may appear, showing the message **Wait while modules are being prepared.** (See Figure 2-10.)

Important

Note that the Module preparation screen will appear only if the firmware in the modules is not 3.0.3. The screen indicates that the software is upgrading/downgrading the firmware to the modules. The next screen you see will be the screen shown in Figure 2-11, the Select Modules screen.

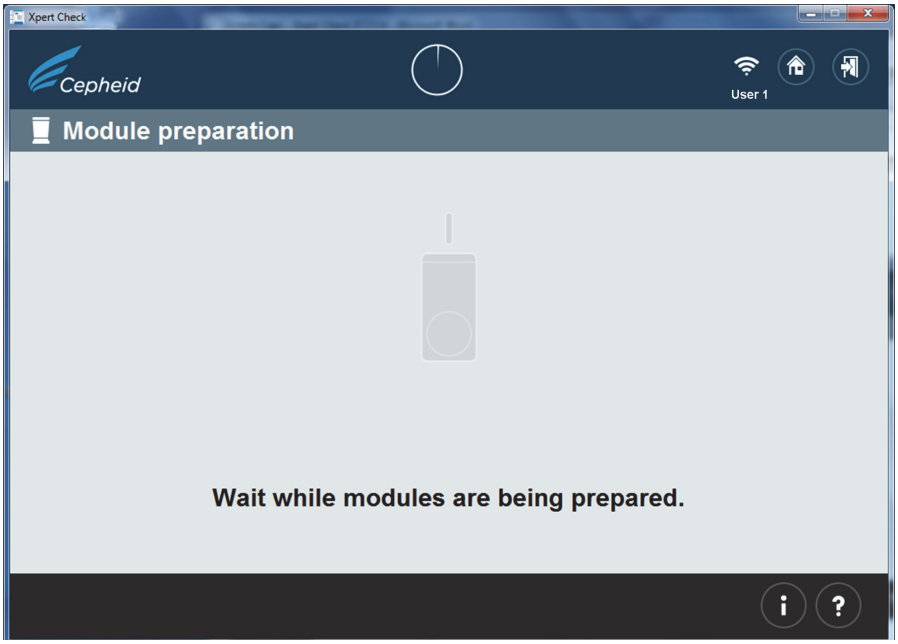


Figure 2-10. Module preparation Screen

12. Follow the on-screen software instructions in Figure 2-11. By default, all detected modules will be marked as selected for checking.

    On this screen, the user can touch or click individual module icons to exclude the modules from being checked, if required. The module icons will disappear as they are excluded.

Note

For excluded modules (not selected for checking), the door position (open or closed) does not matter.

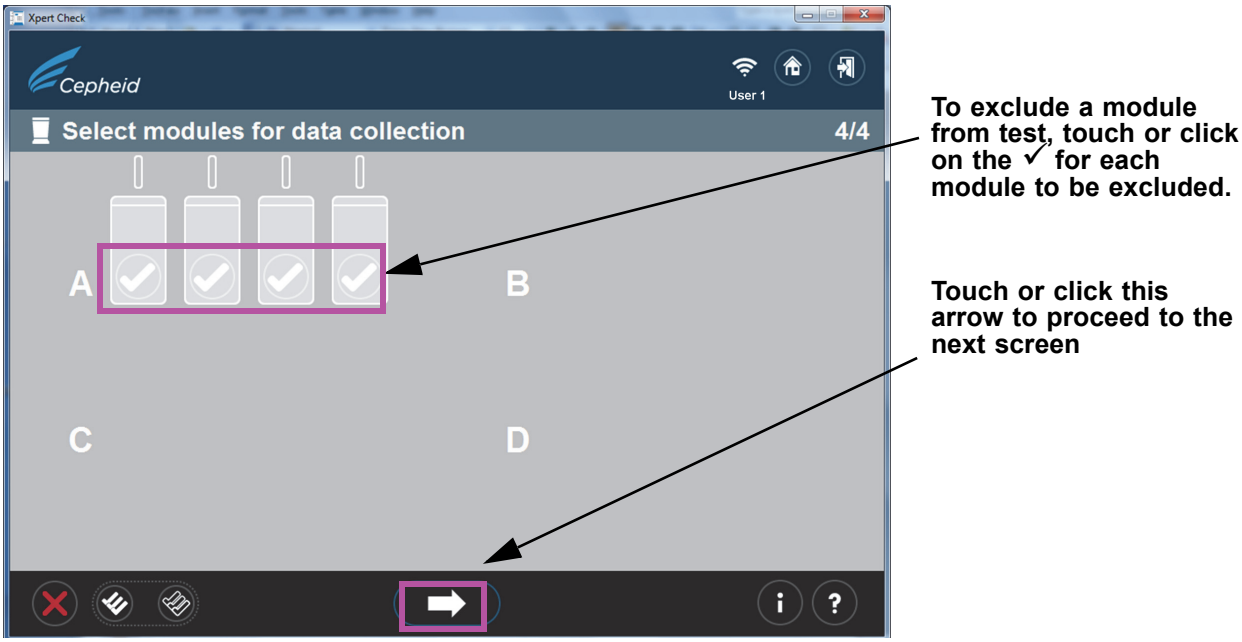


Figure 2-11. Select modules for data collection Screen

Important

GeneXpert-XVI and GeneXpert Infinity systems only: When selecting modules on screen, make a note of which module lights are blinking on the system as you select each bank, to ensure cartridges are placed in the correct modules for testing.

13. After confirming the module selection shown in Figure 2-11, touch or click the white arrow at the bottom of the screen overlay, to begin scanning cartridges. If the module selection shown is incorrect, touch or click the red **X** at the bottom left corner of the screen to return to the Select Modules screen and change your selection. See Figure 2-12.

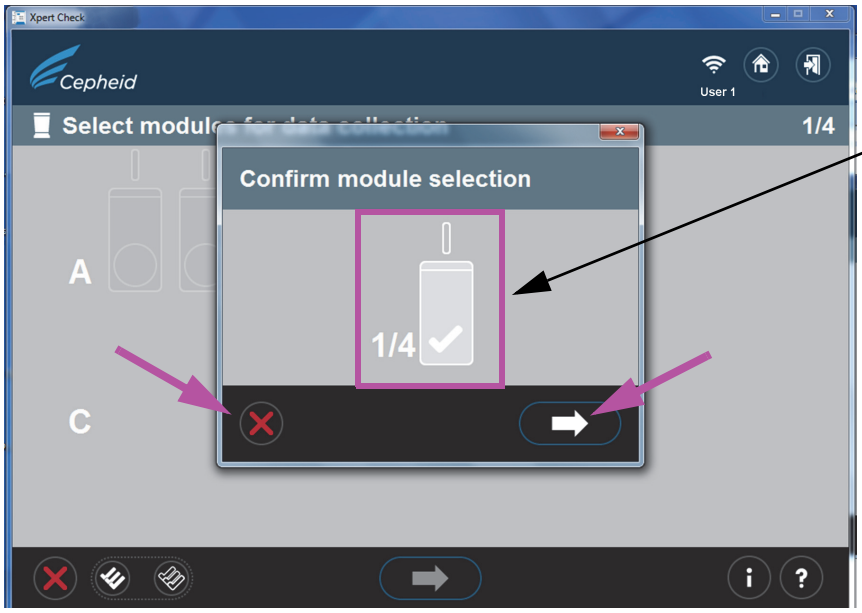


Figure 2-12. Confirm module selection Screen

14. In case of an error in the preceding step, in which either no modules have been selected, or all modules have been excluded, one of the following screens will appear (Figure 2-13). Follow the on-screen instructions to select a module, or start over by returning to the Home screen or exiting the program.

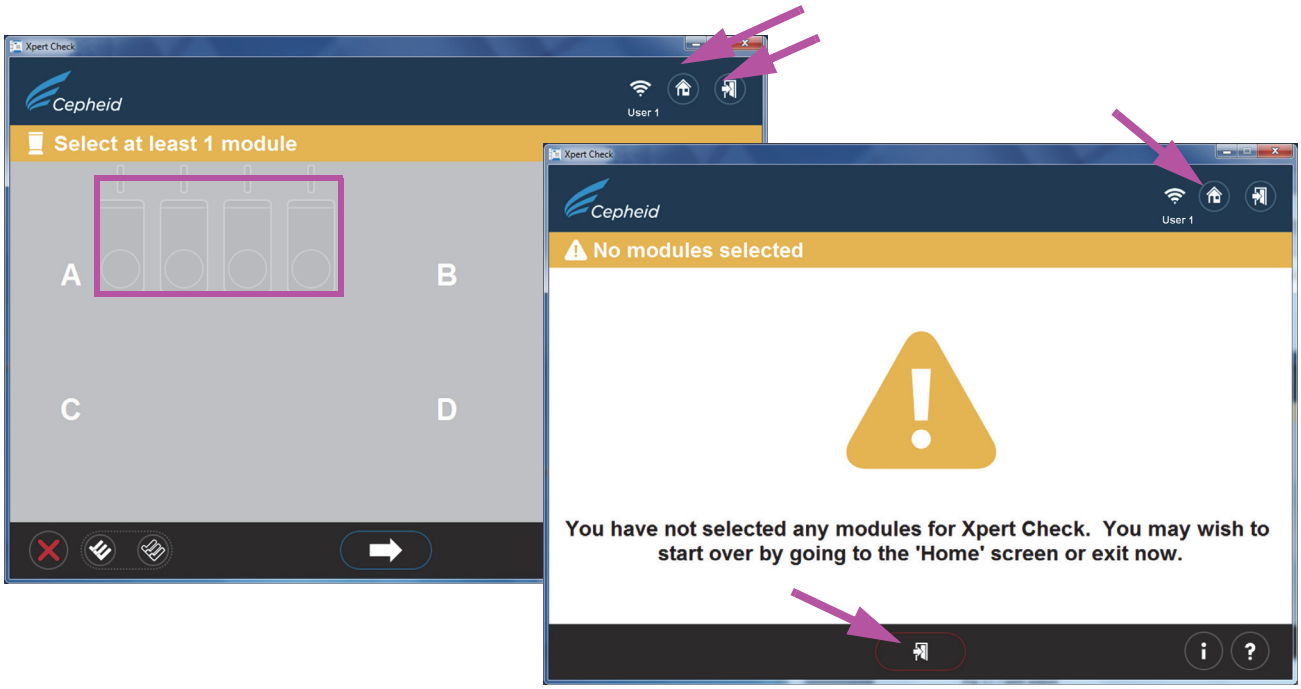


Figure 2-13. Error Screen Examples

15. After confirming your module selection, you will advance to the Scan cartridge screen, where you will be prompted to scan the barcode on the Xpert Check cartridge.

Note Verify you have enough cartridges on hand to perform the check procedure for the desired number of modules.

16. Remove the test kit cartridge from the package for the module you've previously selected, opening only one cartridge at a time.

Important **Allow the cartridge to reach ambient temperature before proceeding. Do not remove a cartridge from refrigerated storage and immediately use the cartridge to run this test.**

17. Scan the cartridge barcode. Figure 2-14 shows a cartridge barcode being scanned. Do not substitute a cartridge with another after it's been scanned.

Note If the barcode cannot be scanned, skip the cartridge and contact your ASP or local Cepheid Technical Support office for a replacement cartridge, if necessary. If the barcode scanner is damaged, missing or incorrectly configured, contact your ASP or local Cepheid Technical Support office for guidance.

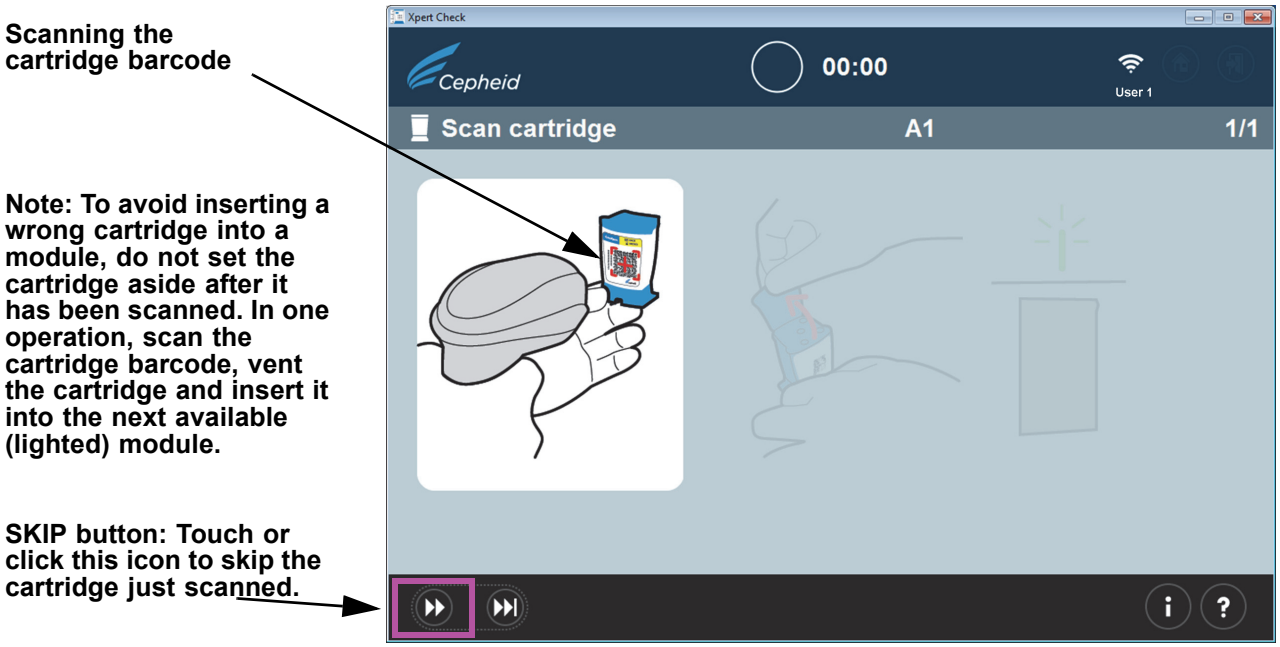


Figure 2-14. Scanning the Cartridge Barcode Screen

A. After scanning the barcode of the cartridge, ensure you open (vent) the cartridge lid and then close it for each cartridge as directed by the software in Step B through Step E below.

Important **Do Not add a sample or reagent to the cartridge. Use ONLY the cartridges in the Xpert Check kit provided.**

Note After a cartridge barcode is scanned a green light will blink on the system above the module door where the cartridge is to be loaded. (See Figure 2-17.)

Note

If, for some reason, you want to skip the cartridge just scanned, touch or click the **SKIP** button at the bottom of the screen. An overlay, shown in Figure 2-15, will appear, asking for confirmation on skipping the cartridge. To SKIP the cartridge, touch or click the forward arrow at the bottom of the confirmation screen. To proceed without skipping the cartridge, touch or click the **X** icon at the left bottom corner of the screen. You are urged to rescan a cartridge (or substitute a new cartridge if necessary) to ensure a module is not skipped.

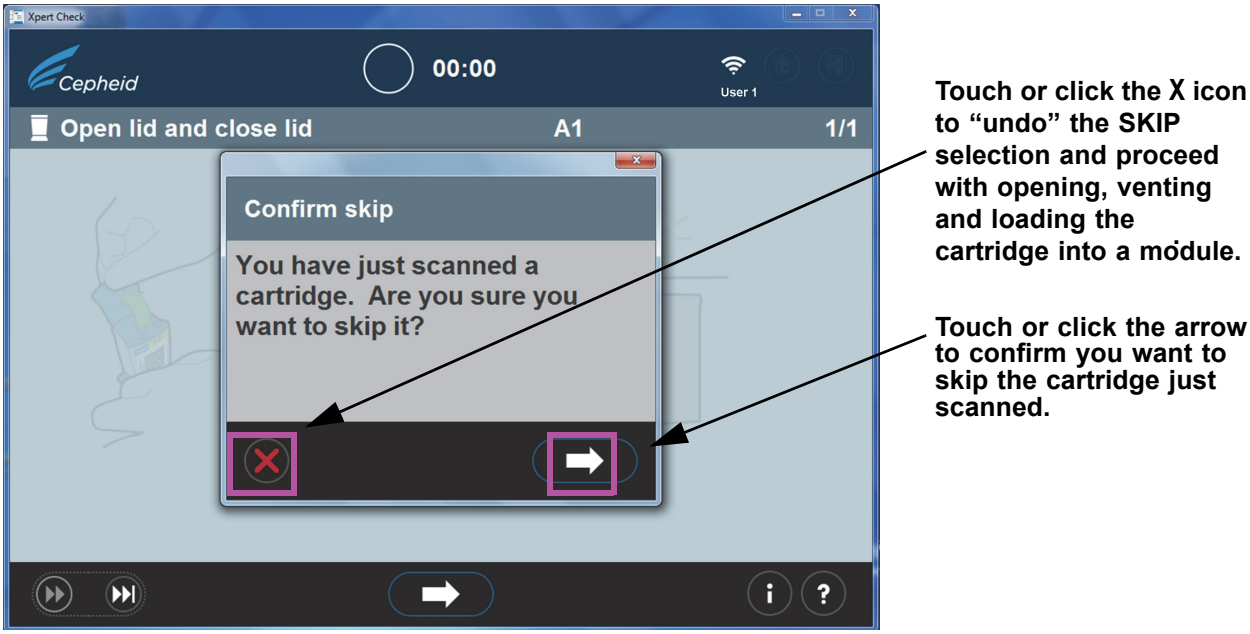


Figure 2-15. Confirm skip Screen

B. Venting the cartridge (shown in Figure 2-16), for two seconds is sufficient. This screen is animated, showing the cartridge lid being opened and closed. After venting, touch or click the forward arrow at the bottom of the screen to continue.

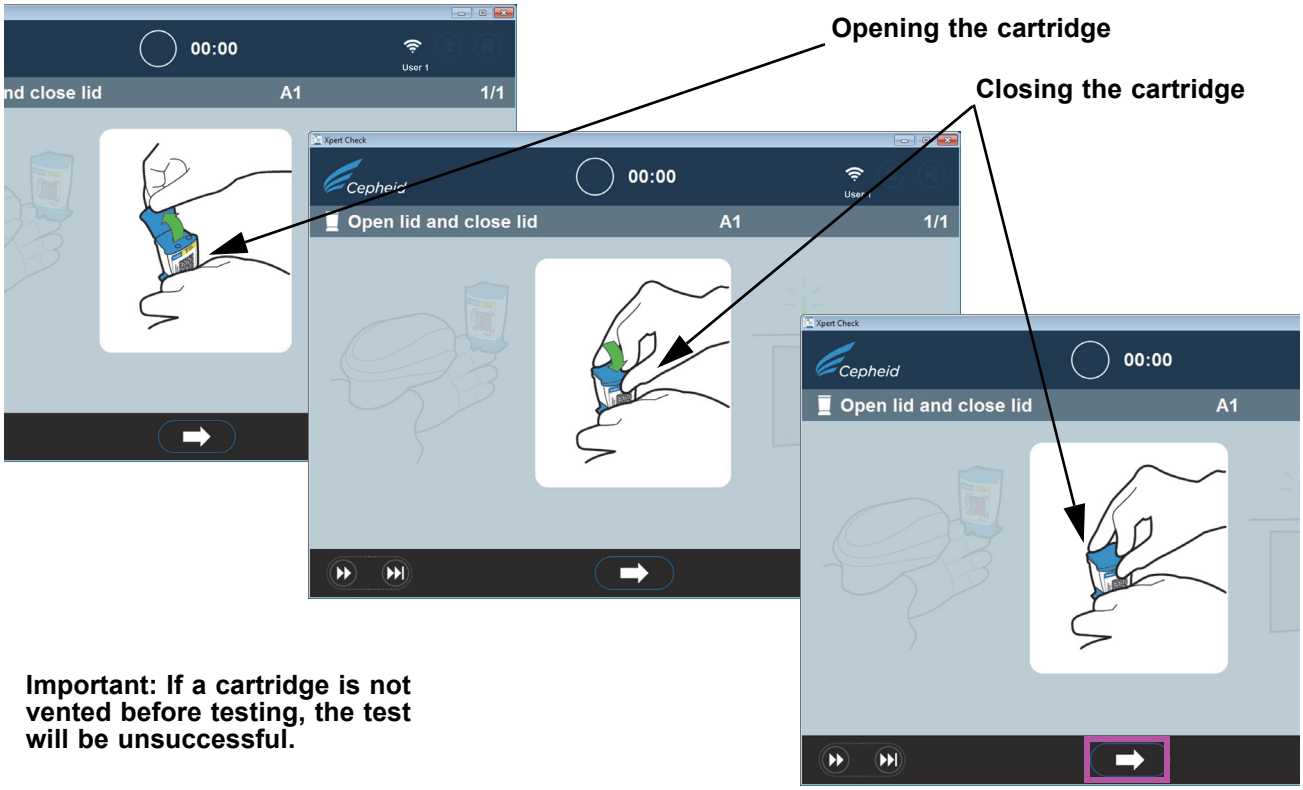


Figure 2-16. Venting the Cartridge by Opening and Closing the Cartridge Lid - Animated Screen

C. Close the cartridge lid and ensure the module door is fully opened to receive the cartridge.

D. Load the cartridge into the module (with the cartridge reaction tube (tab) facing away from you), as directed by the animated software screens. See Figure 2-17.

Note

Be sure to load scanned cartridges in sequence in the next available module. This will avoid loading cartridges in the wrong location or leaving modules empty.

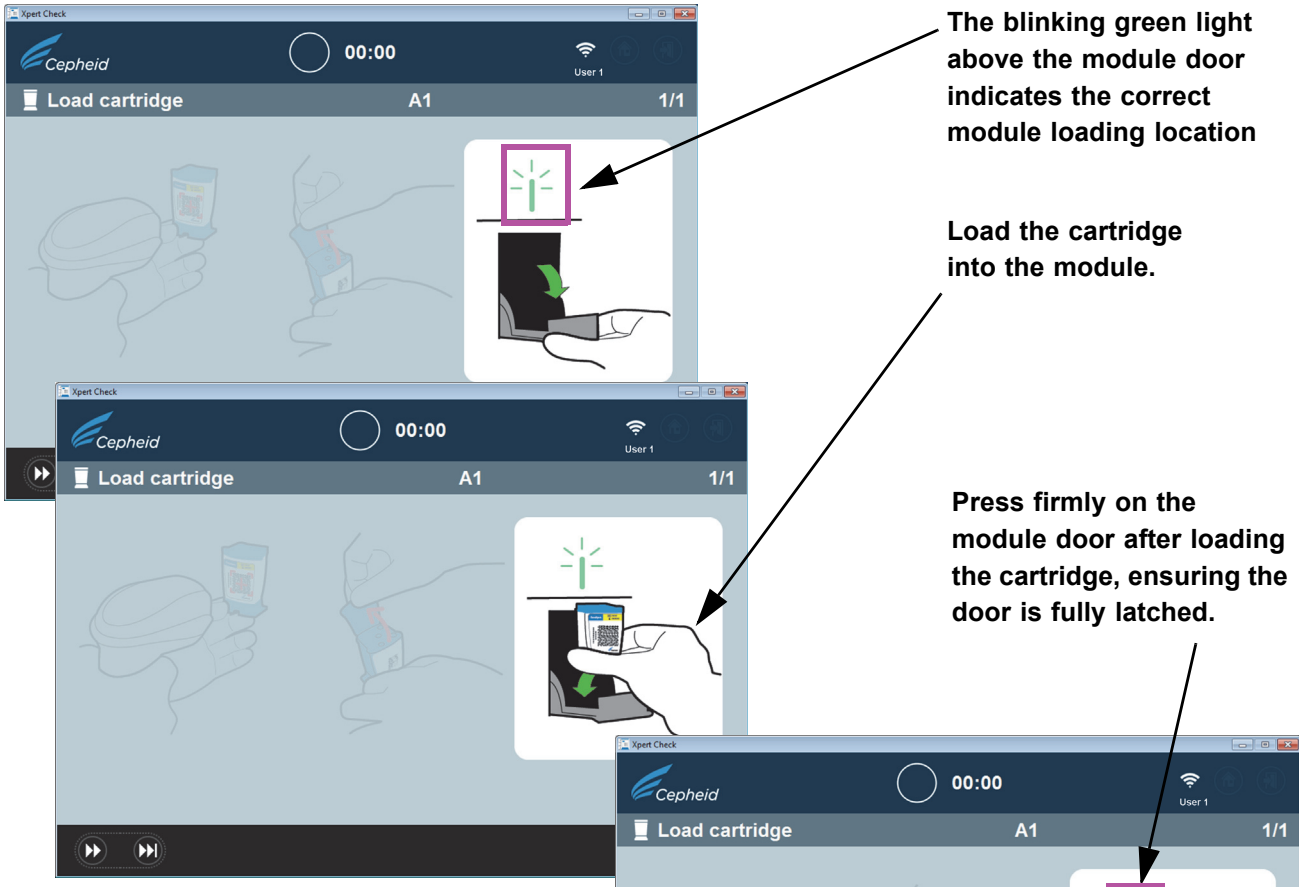


Figure 2-17. Loading the Cartridge into the Module

E. If you are checking additional modules, continue by scanning the next cartridge. Place each individually scanned cartridge into the next selected open module, pressing the module door securely closed until it latches. **As each module door is closed and latched, data collection will automatically start on that specific module.** The blinking green light above the module will then become steady green, indicating that checking has started.

Important

If a module door is not closed completely (until it latches) after loading a cartridge, the screen will continue to display a message to insert a cartridge, and the check will not run.

If you are unable to close and latch a module door after several tries, touch or click the SKIP button at the bottom of the screen to skip the module with the faulty door and move ahead. Notify your ASP or local Cepheid Technical Support office so the module can be serviced.

18. Checking will take approximately 20 minutes to complete after the final module has been loaded for testing. When checking begins, the Data collection in progress screen appears, as shown in Figure 2-18.

Important

If necessary, a retest of a previously run module may be started without waiting for the present module to complete its test, as described in steps 19b through 19d.

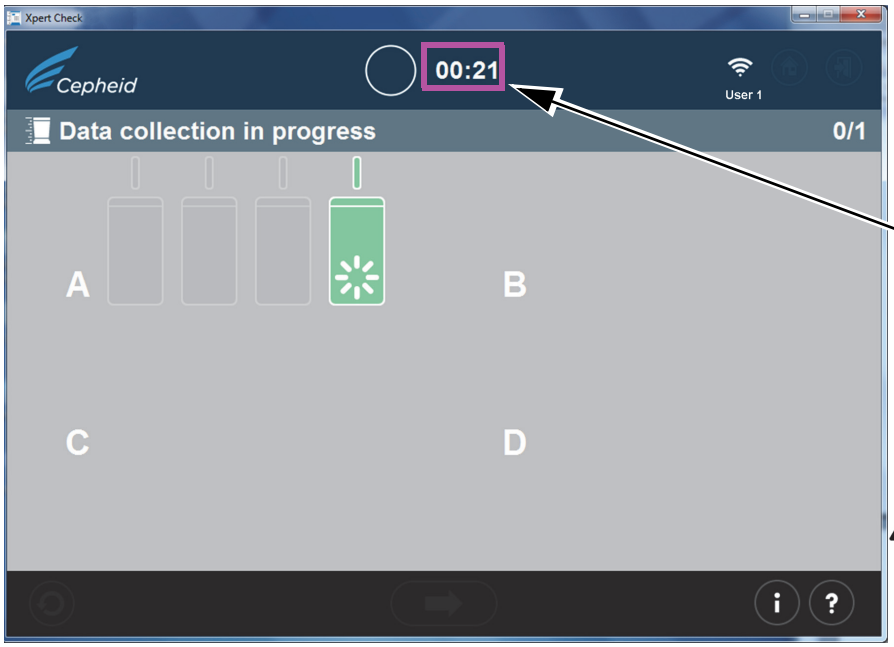


Figure 2-18. Data Collection Screen

Important

If you do not have an internet connection, skip to section 2.2.1 for the remainder of this procedure. If you have an internet connection, continue with step 19.

19. After test completion, the module door will open and the light above the module door will turn off. Screens similar to those shown in Figure 2-19 or Figure 2-20 will appear. Touch or click the right arrow to continue.

    A. Figure 2-19 shows the completion of a successful Xpert Check data collection.

    When the test is complete, touch or click the forward button at the bottom of the screen to begin uploading Xpert Check test results to the Xpert Connectivity Center.

Important

When uploading test results, especially multiple files, verify the selected folder destination is correct.

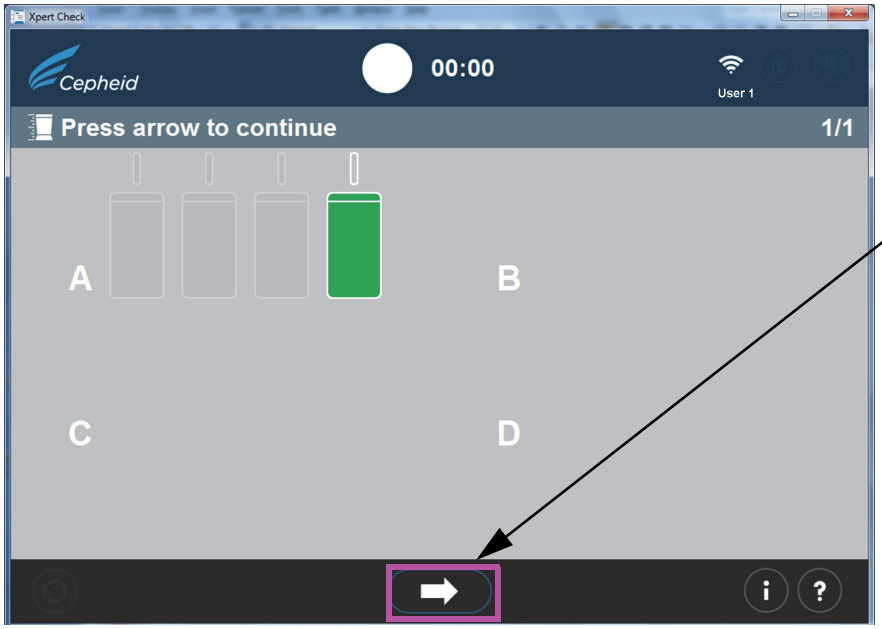


Figure 2-19. Test Completion Screen - Successful

B. If the test was unsuccessful, the screen shown in Figure 2-20 will appear, showing module status. A test retry must be performed. Touch or click the **Retry** icon in the lower left-hand corner of the screen.

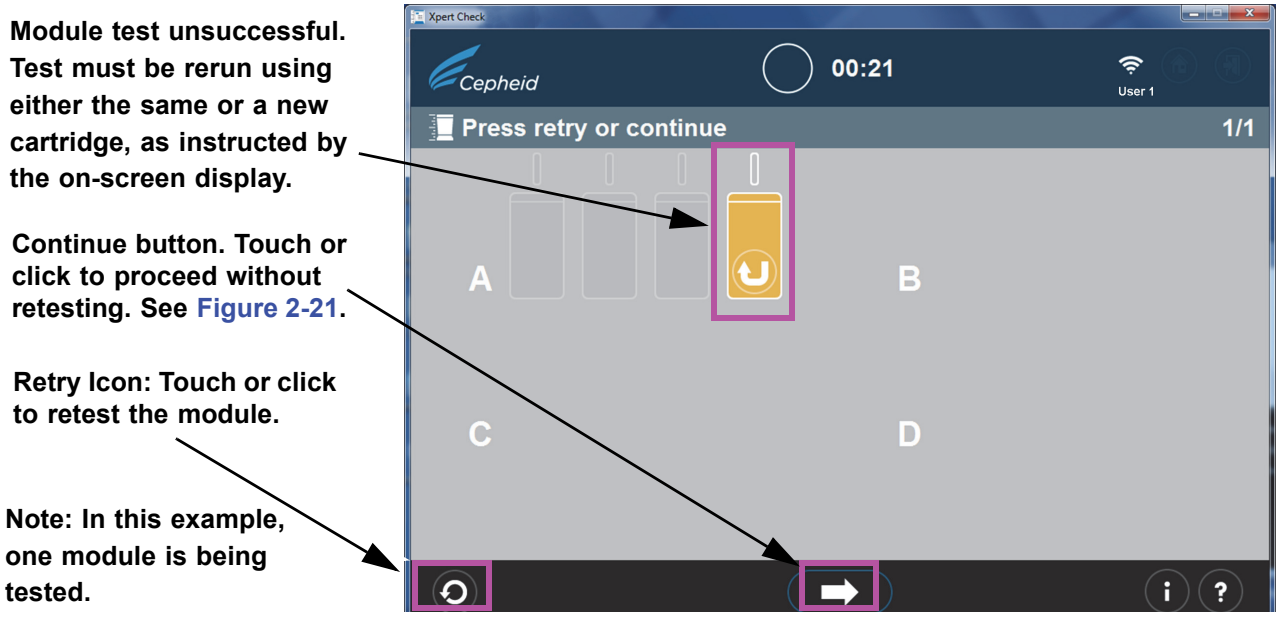


Figure 2-20. Test Completion Screen - Unsuccessful Module Checking Example

C. If the **Continue** arrow at the bottom of the screen is pressed when there is an unsuccessful module test displayed (as shown in Figure 2-20), the Confirm continue screen will appear. See Figure 2-21.

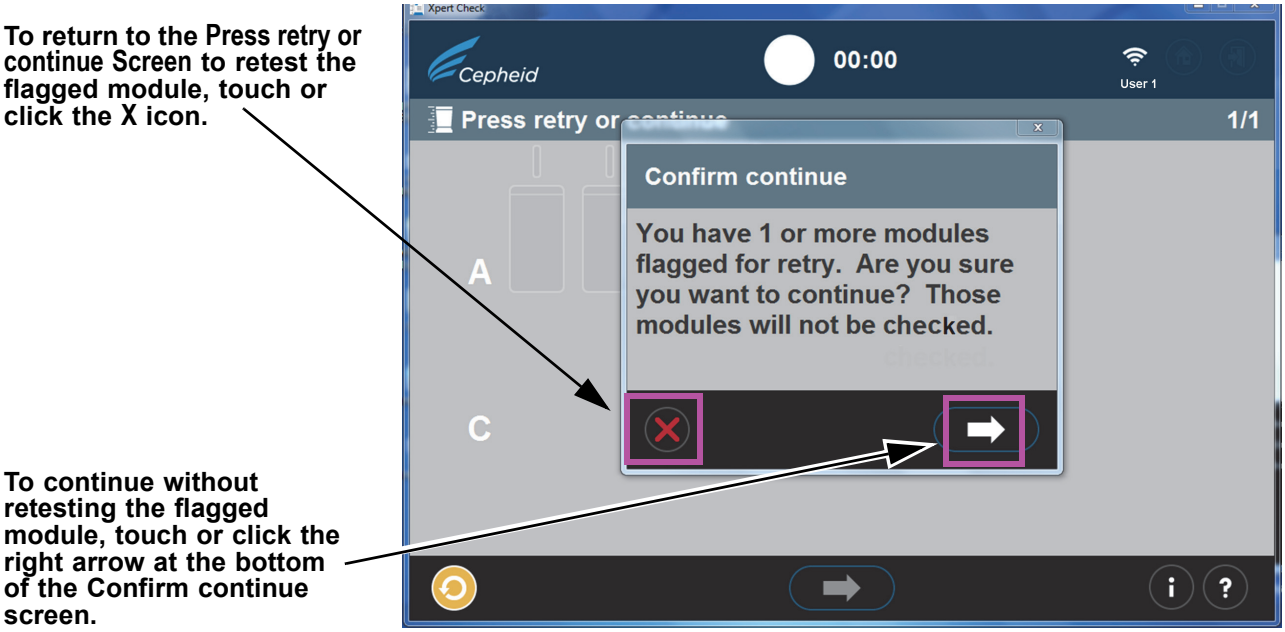


Figure 2-21. Confirm Continue Screen Overlay

You have the option of continuing by touching or clicking the right arrow on the Confirm continue screen overlay. Choosing this option will result in the flagged module not being retested, and you will begin uploading check data as described in Step 20.

Another option is to return to the Press retry or continue screen to Retry (retest) the flagged module by clicking the red **X** icon at the bottom left of the Confirm continue screen. The Retry procedure is described in Step D which follows.

D. If the Retry icon (shown above in Figure 2-21 at the bottom of the screen) appears, touch or click the Retry icon and you will return to the Scan Barcode screen (Figure 2-14) to complete the retest on the affected module(s).

Note that the retest can be of two possible types:

1) Retry with the same cartridge: For example, a message may appear telling you to vent the cartridge, rescan it, and put it back in the module.

2) Retry with a new cartridge: If the cartridge was defective, or had already been used, you will be asked to replace it by scanning the barcode on a new cartridge, venting it, and loading it into the module.

Note

During the course of running retests, modules may need to be skipped if the user runs out of Xpert Check cartridges. Please contact your ASP or local Cepheid Technical Support office for additional Xpert Check cartridges. Rerun Xpert Check on any modules that were skipped.

Note

At the completion of the Xpert Check data collection process, modules determined to require service will be flagged with an orange module icon (See Figure 2-20). Please contact your local ASP or local Cepheid Technical Support office for further assistance in servicing or replacing modules.

20. After successful test completion and Xpert Check data collection, touch or click the forward arrow to display the screen shown in Figure 2-22, if you have an active

internet connection. However, if you have never been internet connected, or have lost your functioning internet connection sometime during the Xpert Check test, a Download Xpert Check code error screen or an Upload incomplete error screen (Figure 2-23) may appear instead, instructing you to write Xpert Check data to a data CD to send to your ASP or local Cepheid Technical Support office. In this case, continue to the instructions beginning at Step 4 (under Section 2.3.1) of this procedure to continue as a user without an internet connection.

Note

With a functioning internet connection, the system should proceed normally (with Step 21), and the Xpert Check code should begin downloading, as shown in Figure 2-24.

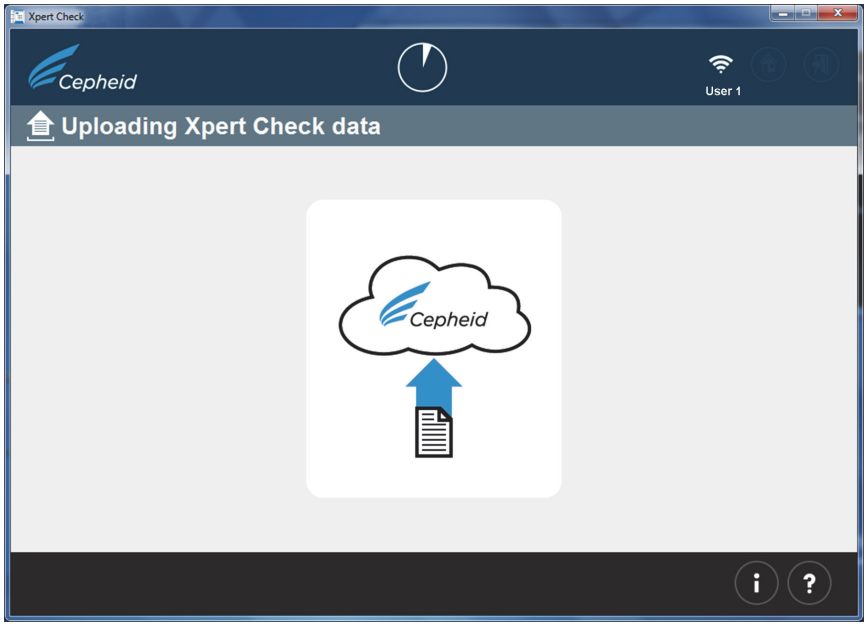


Figure 2-22. Uploading Xpert Check Data Screen

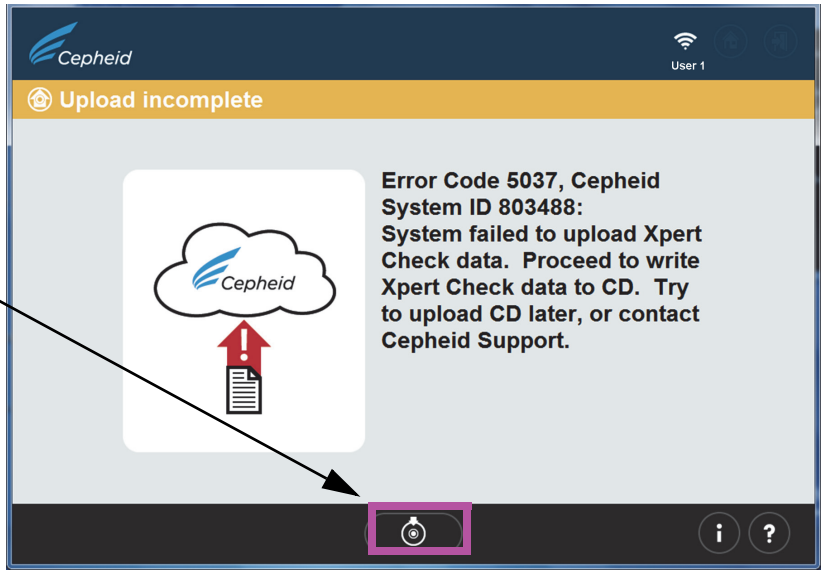


Figure 2-23. Upload incomplete Error Screen

21. When the Xpert Check data has finished uploading, a Quality Assurance check will be performed on the data. If the check is acceptable, the Xpert Check code will automatically download. See Figure 2-24.

    If the test is not acceptable, the affected module(s) will require service or replacement and will be flagged with an orange icon. Please contact Cepheid or your local ASP or the local Cepheid Technical Support office for further assistance.

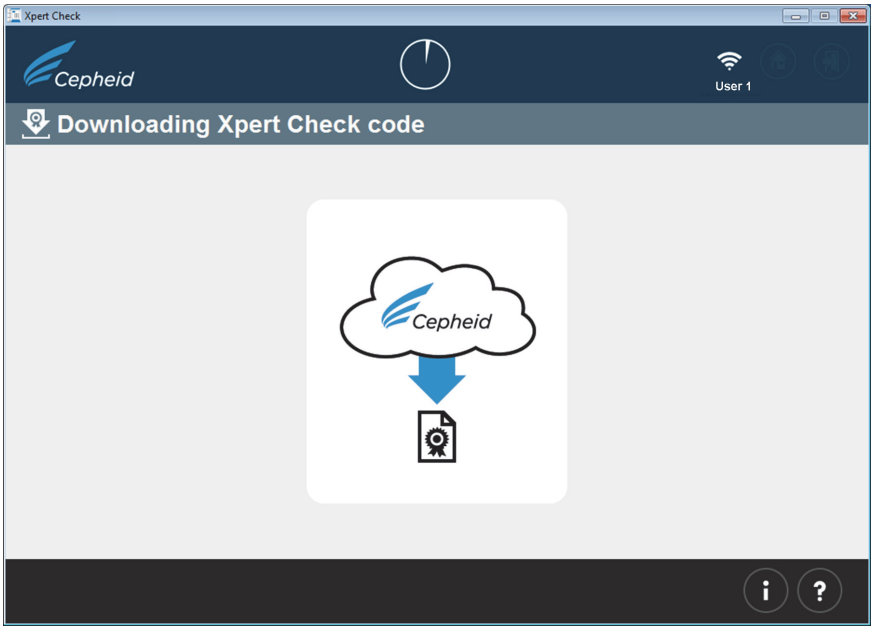


Figure 2-24. Downloading Xpert Check code Screen

22. After the Xpert Check test results have downloaded, the Xpert Check code will be applied to each successfully tested module, and those modules will then be identified with a **+** symbol. See Figure 2-25. As shown here, one module is being checked.

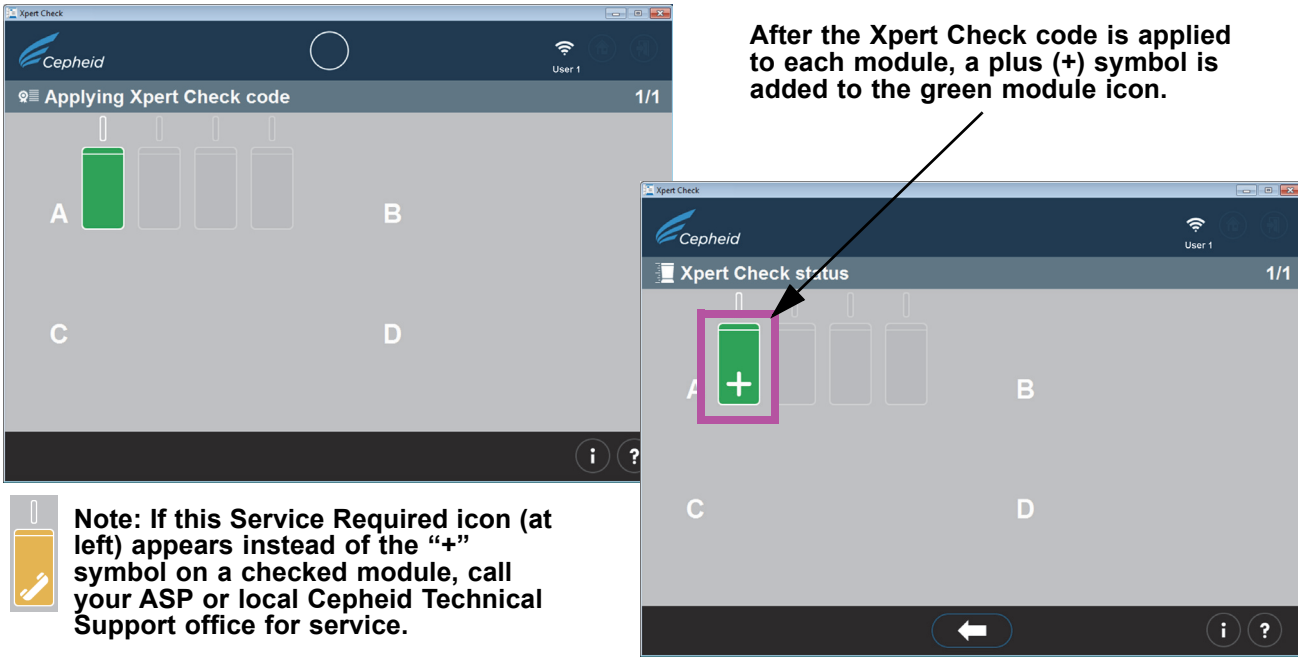


Figure 2-25. Applying Xpert Check code Screen

Note

In the screen shown in Figure 2-25, some modules may display the service required icon or may be grayed out if they were skipped.

23. After all the Xpert Check codes have been applied to the successfully-tested modules (those green modules which appear with the plus symbols applied), the Xpert Check complete screen will appear. See Figure 2-26. This screen shows the location of the Xpert Check Data report, which is available for review, if desired.

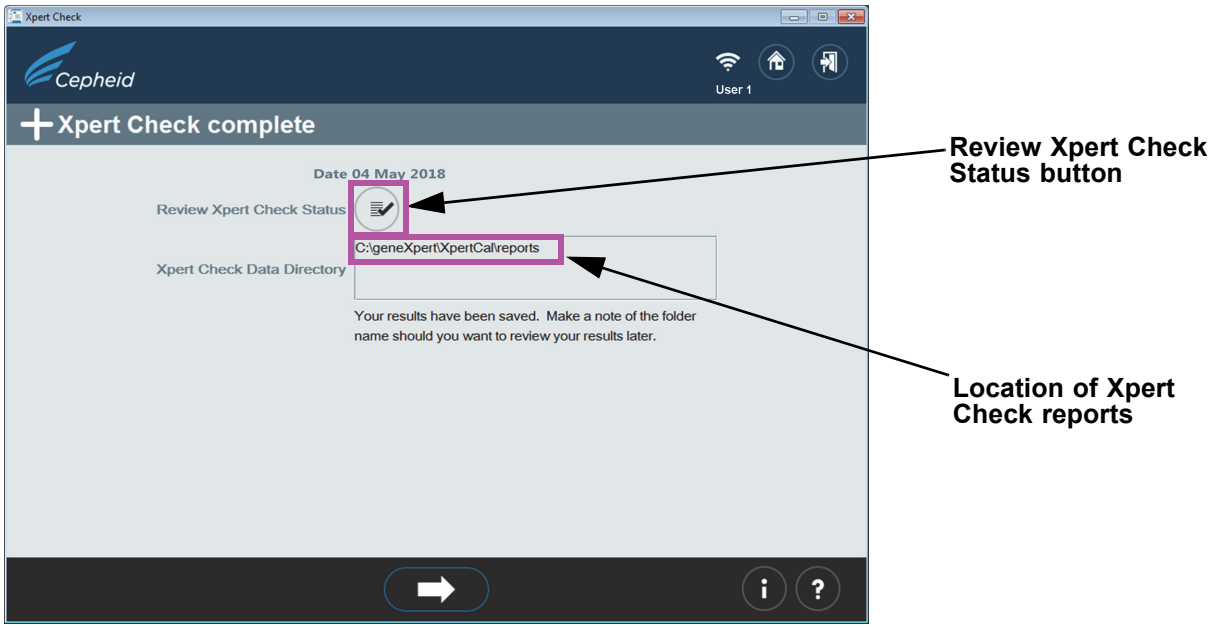


Figure 2-26. Xpert Check complete Screen

24. Remove and discard all Xpert Check cartridges. Do not save partial kits (all unused cartridges must be discarded).When complete, click the **Exit** icon at the top or bottom of the screen to exit the program. See Figure 2-27.

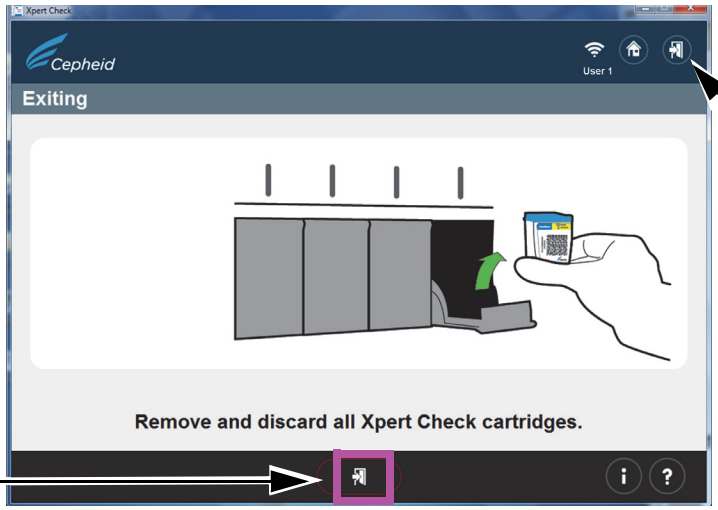


Figure 2-27. Exit the Program

25. The screen shown in Figure 2-28 appears only if you touch or click the exit arrow in the upper right of the screen.

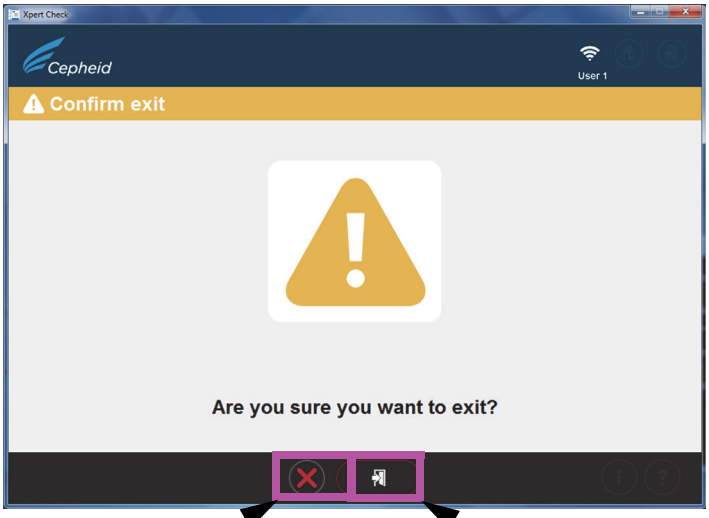


Figure 2-28. Confirm exit Screen

This completes the Xpert Check Test for an internet-connected user.

Note Contact your Authorized Service Provider or the local Cepheid Technical Support office concerning modules requiring service.

Note To view your Xpert Check results, see Step 23 and Figure 2-26, which shows the file path and location of Xpert Check results and the Xpert Check Summary report.

2.3.1 Xpert Check Completion For Non-internet Connected Users

For Non-internet connected users, you should have completed Step 1 through Step 19 of Section 2.3 to collect data before starting this section.

1. This section begins with the Data collection in progress screen, which is similar to Step 18 in Section 2.3, and the screen shown in Figure 2-18 for internet-connected users.

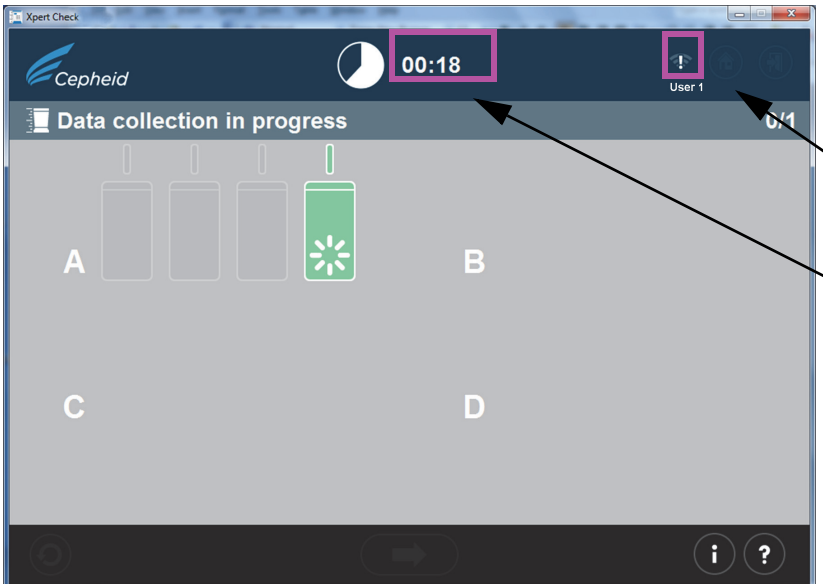


Figure 2-29. Data collection in progress Screen

2. After test completion, the module door will open and the light above the module will turn off. A screen similar to that shown in Figure 2-30 will appear. Touch or click the right arrow at the bottom of the screen to advance to the next screen.

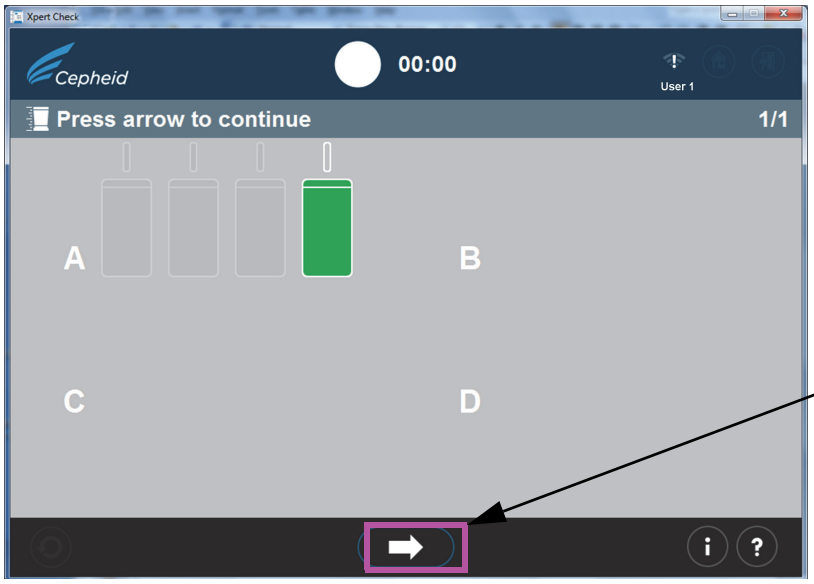


Figure 2-30. Test Completion screen - Successful

3. When the Write Xpert Check data to CD screen appears (Figure 2-31), you will be prompted to press the **Eject** button on the DVD drive to remove the existing Xpert Check Software CD so you can insert the blank data CD.

Note In the following step, use care in inserting the blank CD into the DVD drive. Be sure the CD is fully seated in the tray before closing the drive door.

Important **If you have been running this test as an internet-connected user and then lose your internet connection and received an error screen (Figure 2-23), resume your procedure beginning with the following Step 4, continuing through Step 12.**

Note In the following step, pause for 10 seconds after CD insertion and cancel any wizards that auto-open before touching or clicking the forward arrow to proceed. When you either close the wizard or have waited enough time to ensure that a wizard will not auto-open, touch or click the forward button to proceed. This will launch the Windows CD burning screens that the Xpert Check program opens.

4. Insert the blank CD into the DVD drive of the computer and close the DVD drive tray fully to ensure the CD will be recognized.

   Pause to allow the launch of any possible CD wizard programs. If wizard programs launch, close them before touching or clicking the forward button to proceed.

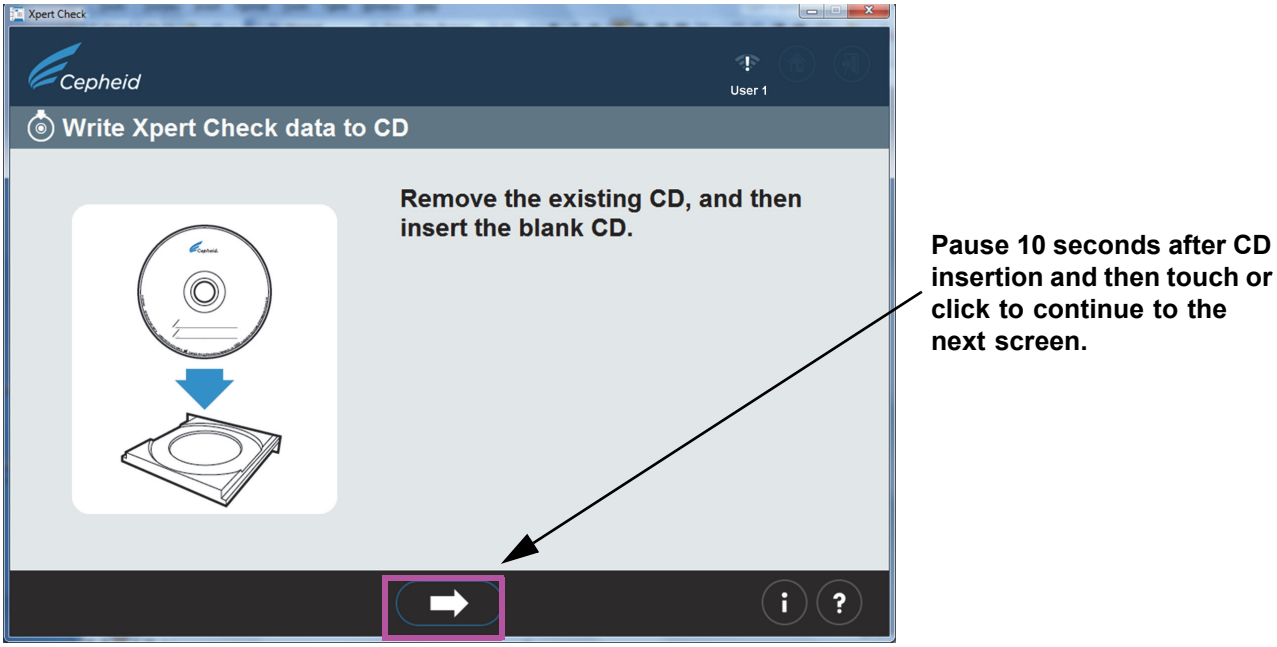


Figure 2-31. Write Xpert Check data to CD Screen - Step 1

5. After inserting the blank CD, the screen will change briefly, indicating the CD has been recognized. See Figure 2-32. This screen will remain displayed until the CD writing process is complete.

Note It is not necessary for the user to locate the file to write because that process is automatic.

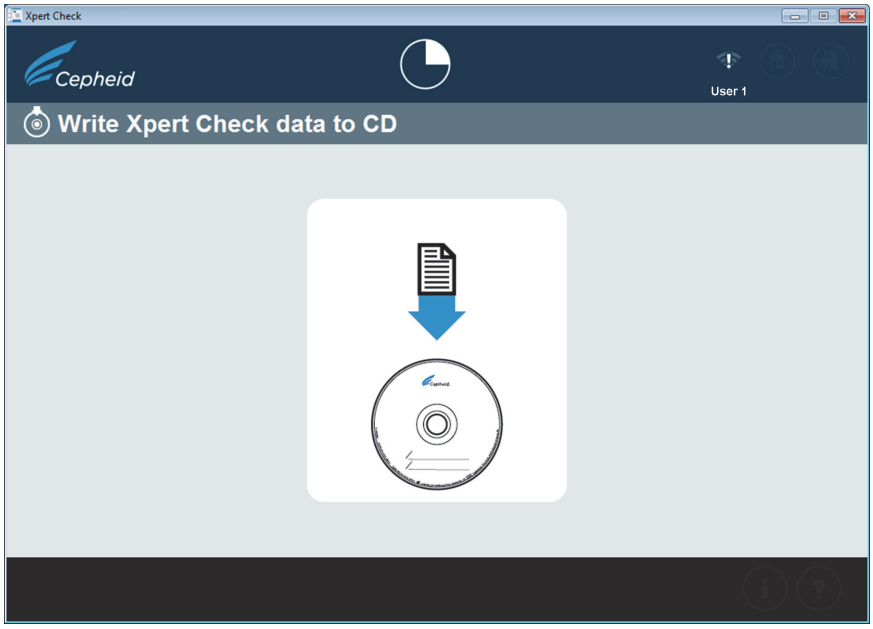


Figure 2-32. Write Xpert Check data to CD screen - Step 2

6. The CD Writing Wizard or Burn to Disc screen (Figure 2-34) will then appear as an overlay of the screen shown above, in Figure 2-32.

   The next screens (Figure 2-33 though Figure 2-37) show the CD writing program screens as you progress through the writing process.

   - Windows® 7 users: Follow the screens on the top of the figure.
   - Windows®10 users: Follow the screens at the bottom of the figure.

   A. On the first screen, after successful recognition of the blank CD, you will be asked to provide a name for the CD that you will be writing. DO NOT simply touch or click the **Next** button to continue the writing process with the default name that appears. Instead, type in your facility's name, such as "XYZ Hospital," in the space provided and touch or click **Next**. See Figure 2-33.

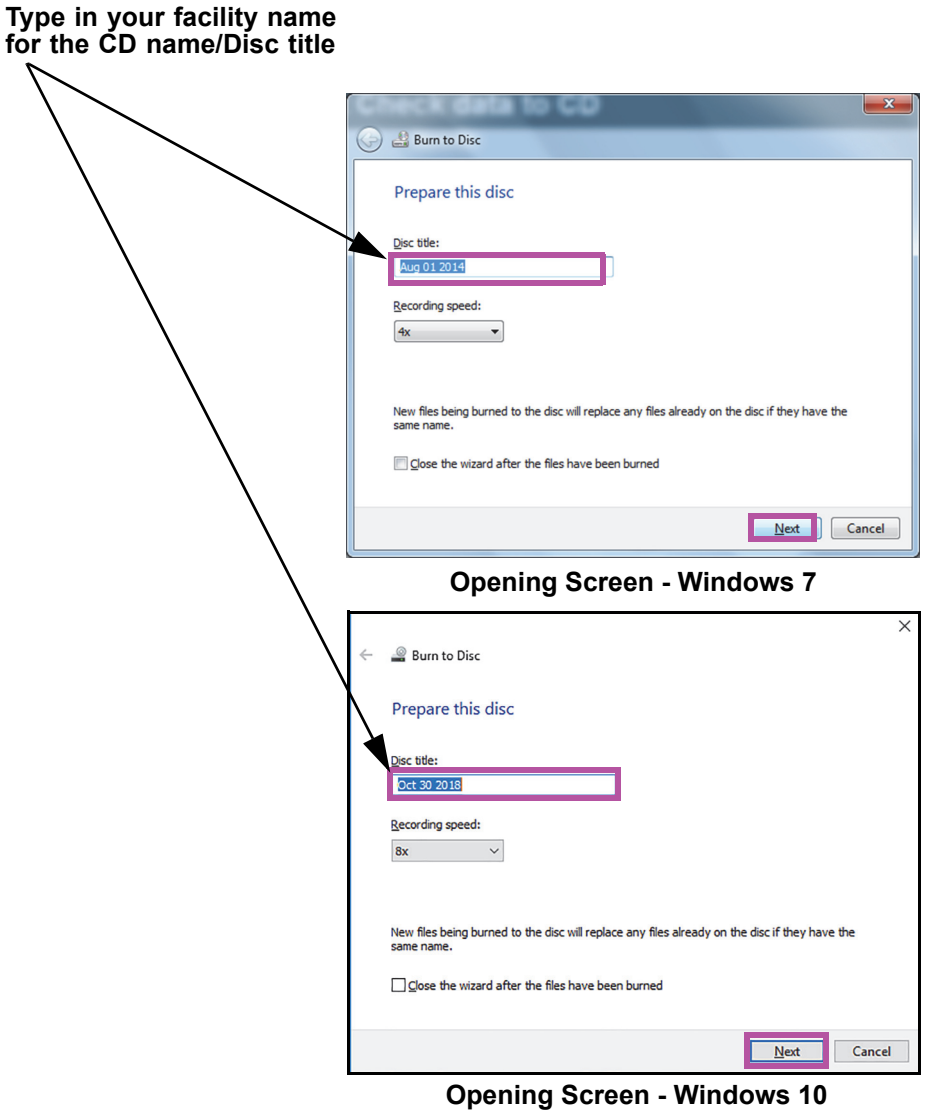


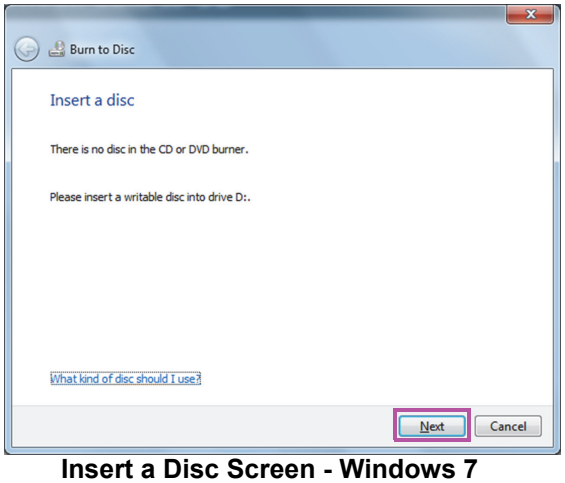
Figure 2-33. CD Writing Program - Opening Screen

B. If the CD is not recognized, the screen shown in Figure 2-34 may appear, instead of the screen in Figure 2-35, asking you to insert a writable disc to continue. Writable discs, in this case, are CDs on which you can store files. Writable discs can only be written to once, meaning that once any files are copied to the disc, they are there permanently.

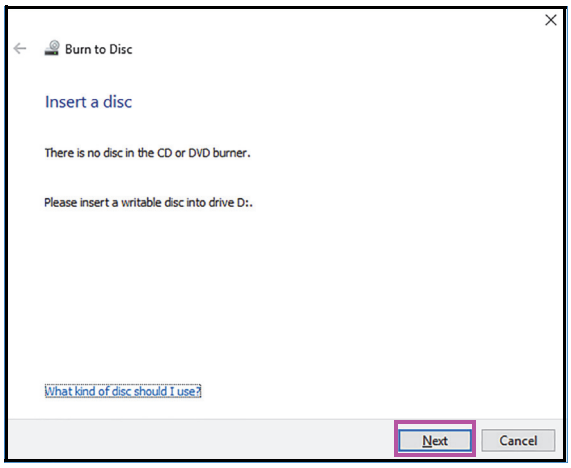
   A disc that has data on it is not considered to be a writable disc and will result in an error screen, as shown in Figure 2-39.

Note

If you are unsuccessful with any part of the CD writing process, you may contact your ASP or local Cepheid Technical Support office for assistance. It is safe for you to close the Xpert Check software now because the Xpert Check files have been saved to the hard drive and you will not lose data.



Insert a Disc Screen - Windows 7

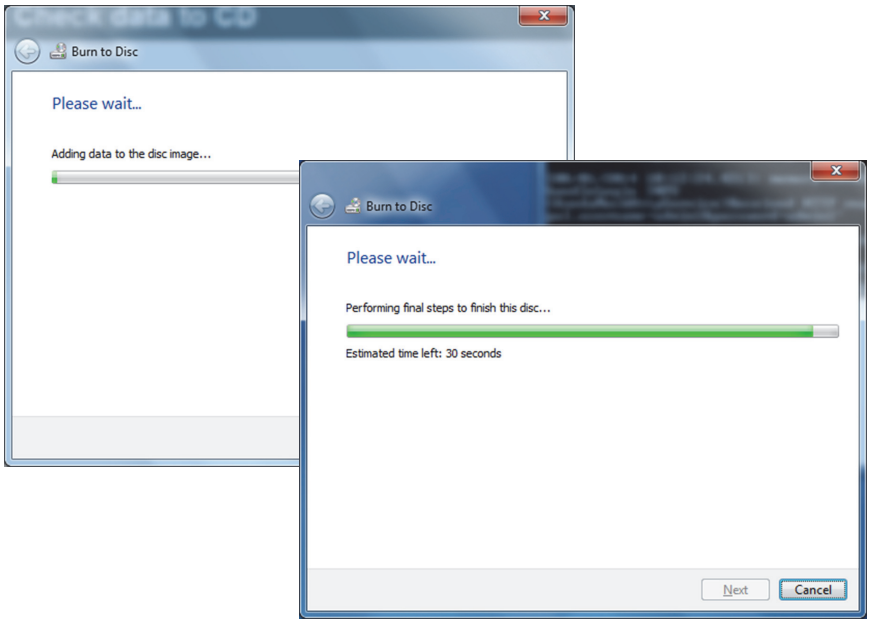


Insert a Disc Screen - Windows 10

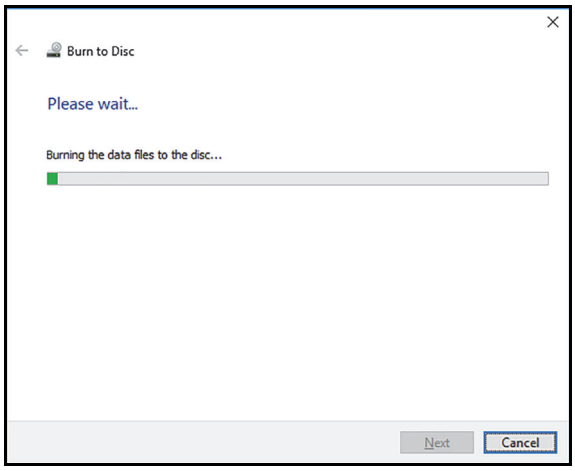
Figure 2-34. CD Writing program - Insert a writable disk to continue Screen - Example

C. After successful recognition and naming of the CD, touch or click the **Next** button to continue. The writing process will begin automatically.

D. During the writing/burning process, a progress bar will appear on the screen. See Figure 2-35.



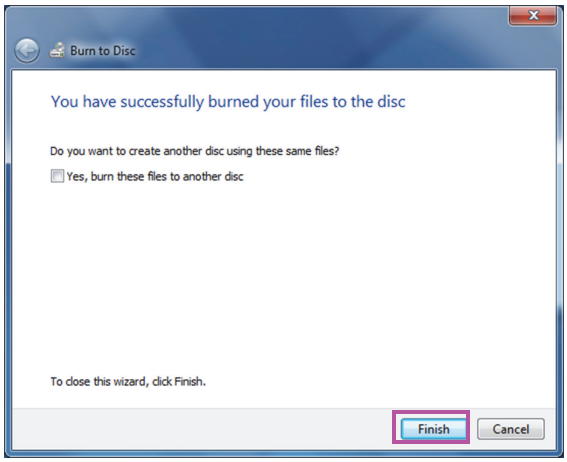
File Burning Progress Screens - Windows 7



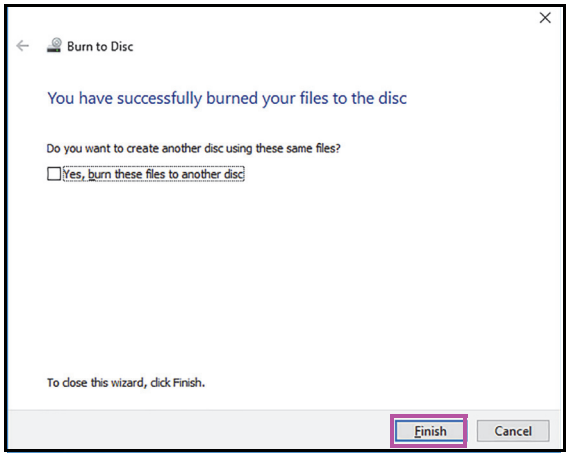
File Burning Progress Screen - Windows 10

Figure 2-35. CD Writing/Burning Progress Screen

E. When the writing of the CD is complete, the screen shown in Figure 2-36 will appear. Touch or click the **Finish** button to exit the CD writing program.



Completion Screen - Windows 7



Completion Screen - Windows 10

Figure 2-36. CD Writing Completion Screen

F. On a Windows 7 computer, you may see the screen displayed in Figure 2-37 after a successful CD write. Touch or click the **OK** button as many times as necessary for the screen to disappear, before continuing.

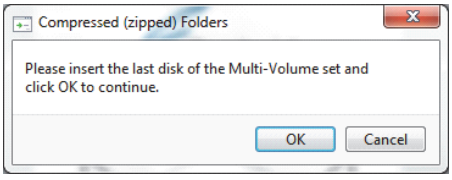
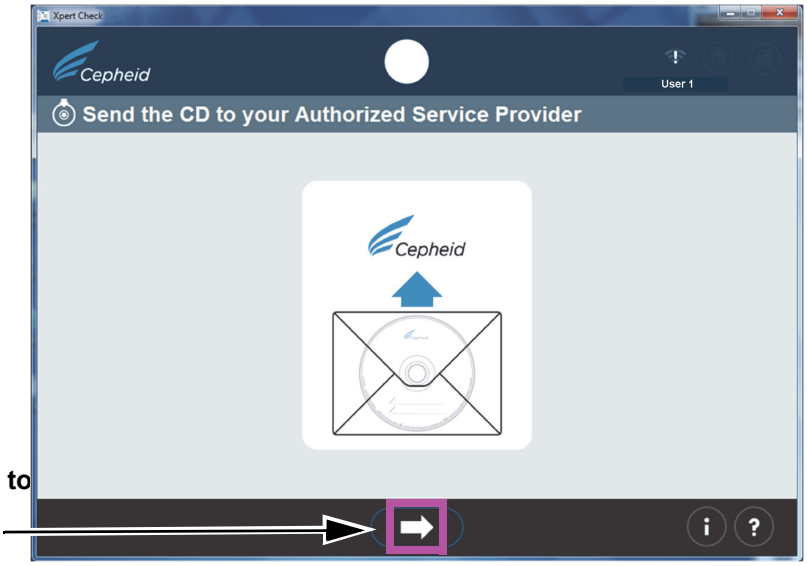


Figure 2-37. Final Screen from Windows 7 After CD Writing has Completed

7. After touching or clicking the **Finish** button on the CD writing screen, the Send the CD to your Authorized Service Provider Screen will appear (see Figure 2-38). Remove the completed Xpert Check data CD from the disk drive and prepare the label, as described in Step 10.



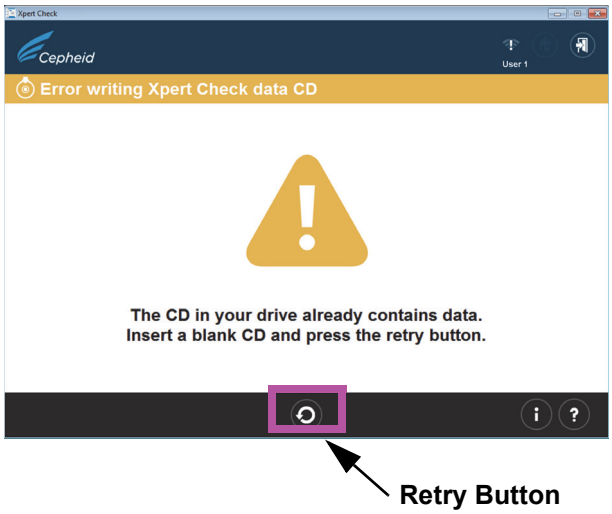
Touch or click to proceed to the next screen, prior to shutdown.

Figure 2-38. Send the CD to your Authorized Service Provider Screen - Step 3

8. If a problem has occurred anytime during the CD writing process, an error code screen may appear. (See Figure 2-39).

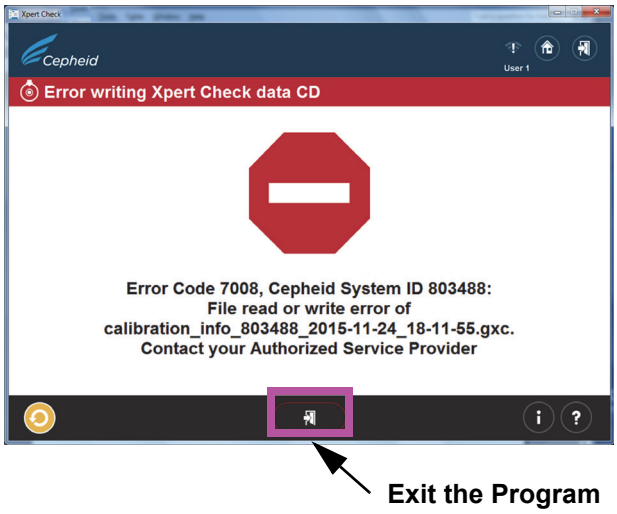
   - If a CD you have inserted already contains data as shown in the error screen below at the left, remove the CD and insert a blank CD, and then touch or click the **Retry** icon.
   - In the case of a read or write error, the screen shown at the right may appear and you must exit the program. Contact your ASP or the local Cepheid Technical Support office for assistance, if necessary.

Disc is not Writable (Already Contains Data)



Retry Button

General Write Failure



Exit the Program

Figure 2-39. Error writing Xpert Check data CD Screens - Two Examples

9. After test completion, the Exiting screen will appear with the message **Remove and discard all Xpert Check cartridges** (see Figure 2-40).

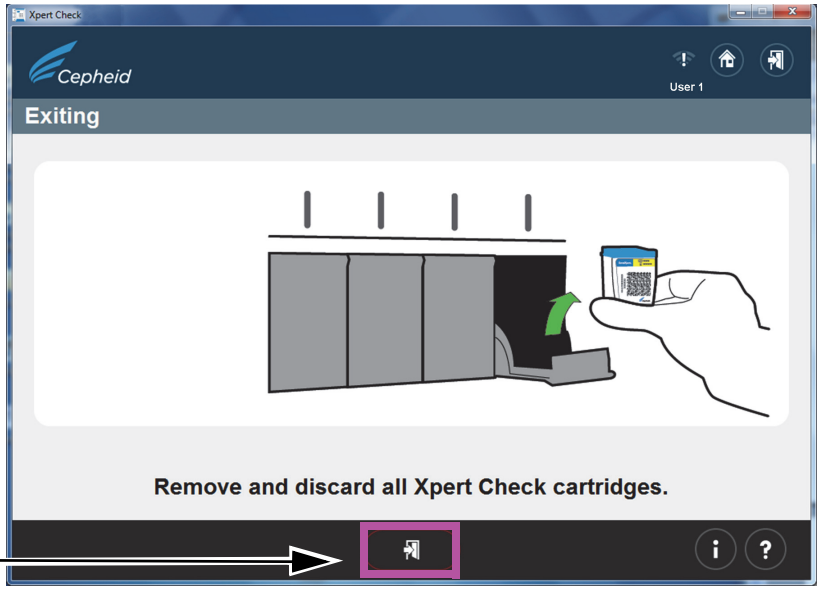
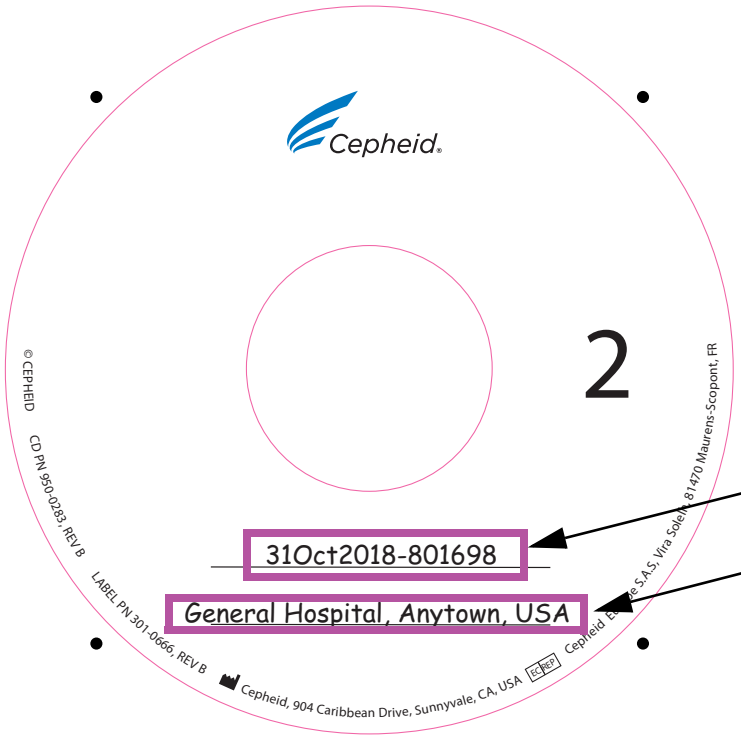


Figure 2-40. Exiting Screen

10. Use a felt-tip pen to write on the label of the Xpert Check data CD you have just created by writing the date, instrument identification and facility/location of the test performed. See a label example in Figure 2-41.



Note: It is the responsibility of the user to properly enter the date, instrument identification, facility name and location on the Data CD label.

Failure to properly label your Data CD may result in lost data and a delay in obtaining your module Xpert Check code test.

Date-Instrument Identification

Facility, Location

Figure 2-41. Data CD Labeling Example

11. You have the option to copy the calibration_info.gxc data file (located on the Xpert Check data CD just written) and Email the data file directly to your ASP or the local Cepheid Technical Support office instead of mailing the CD. If Email is not an option, place the Xpert Check CD2 into the provided CD shipping envelope and mail it to your local Authorized Service Provider (ASP) or the local Cepheid Technical Support office for data quality assurance checking and the issuing of your Xpert Check code.
12. Your ASP or the local Cepheid Technical Support office will perform the quality assurance review and, if successful, send back your Xpert Check code either by Email or regular mail, depending on what method you have previously set up with them.

Note Discard all remaining materials from the kit. DO NOT save unopened kit pouches for later use. DO NOT discard your Software CD. For users who Emailed their file and have not shipped their data CD: DO NOT discard your Data CD.

13. Restart your GeneXpert Dx, GeneXpert Xpress or GeneXpert Infinity system and computer.

Note You can continue to use your system while awaiting your Xpert Check code.

2.3.2 Obtaining the Xpert Check Code for Non-Internet Connected Users

Note Ensure the system is in the same configuration as when Xpert Check was run (i.e., no software updates or changes have been made and no new GeneXpert systems have been moved to or from this computer). In the case of any module servicing and/or replacement that may occur between data collection and application of the Xpert Check Code, new or modified modules will be ignored for the purposes of the Xpert Check testing process.

Note In the following step, use care in inserting the CD into the DVD drive. Be sure the CD is fully seated in the tray before closing the drive door.

1. Exit the GeneXpert Dx, GeneXpert Xpress or GeneXpert Infinity software.
2. To finish the Xpert Check process, place the Software CD in the DVD drive of the computer connected to the GeneXpert Dx or GeneXpert Xpress instrument or in the kiosk computer for the GeneXpert Infinity.
3. Touch or click on My Computer, then touch and hold or double-click on the applicable drive letter for your DVD drive. The files located on the CD will then be displayed. Find and touch and hold or double-click the **XpertCheck.exe** application/ shortcut to launch the software.
4. Log in with your GeneXpert Dx, GeneXpert Xpress or GeneXpert Infinity designated **USER NAME** and **PASSWORD** (see the IMPORTANT note in Section 2.1). Also see Figure 2-4 for the Login screen.

   After entering your login information, touch or click the forward arrow button at the bottom of the screen to advance to the next screen (the Xpert Check Home screen).

Note

The user name and password are the same ones you used for the GeneXpert Dx, GeneXpert Xpress or Xpertise software. If an ASP (FSE) previously performed Xpert Check and is not now on site, the user name and password should have been provided for this step to enter the code. If the user name or password are not now available, contact your ASP or your local Cepheid Technical Support office.

5. Touch or click the **Enter Xpert Check Code** button. See Figure 2-42. The Enter Xpert Check code screen will appear. See Figure 2-43.

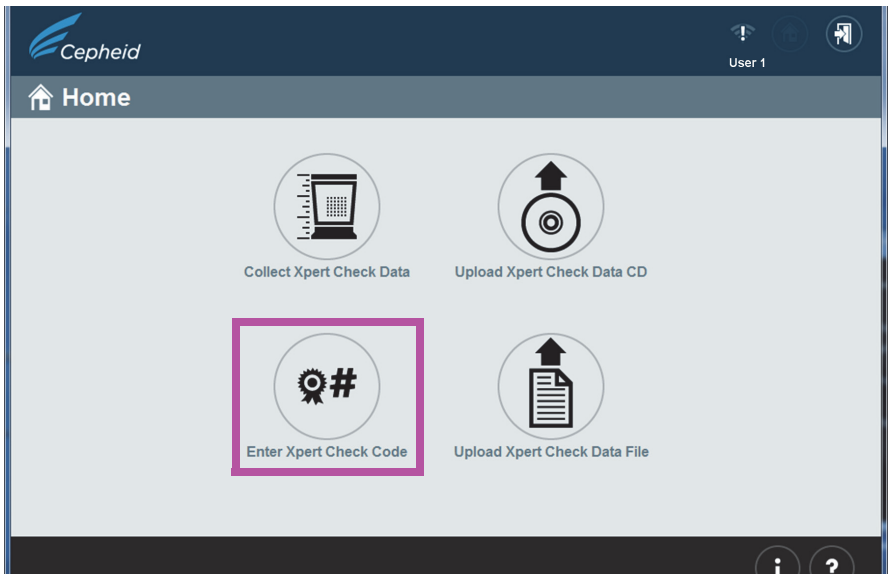


Figure 2-42. Home Screen, showing Enter Xpert Check Code Button

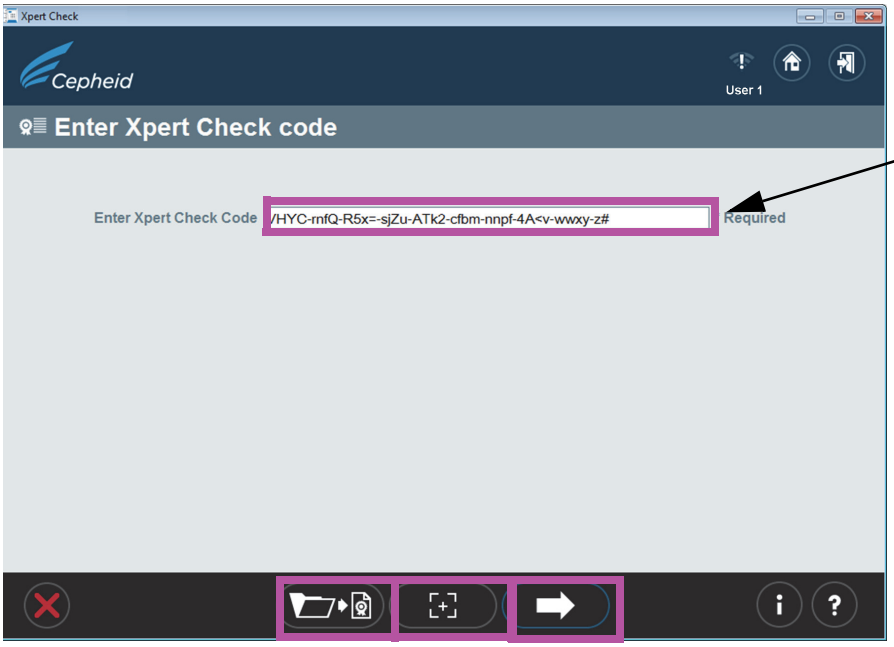


Figure 2-43. Enter Xpert Check code Screen

6. Enter your Xpert Check code as described below.

   In this step, there are various ways to enter the Xpert Check code, depending on your system. Your four options are listed below.

   A. Option 1 (For GeneXpert Dx or GeneXpert Infinity systems only): Use your scanner to input the barcode as follows: First, click the icon located in the bottom center of the screen. The Xpert Check Code File (Figure 2-44) will appear on your screen. Position your scanner to scan the barcode on the Code form, using care to avoid any reflection on the monitor that may interfere with your scanner. See Figure 2-44 for an example of an Xpert Check Code File.

   B. Option 2 (For all systems): Print a copy of the Xpert Check Code File and use your scanner to scan the barcode on the printed page. See Figure 2-44 for an example of an Xpert Check Code File.

   C. Option 3 (For GeneXpert Dx and GeneXpert Infinity systems only): Copy and paste the code string into the Enter code screen from the screen's display. The code string is visible on Figure 2-44.

   D. Option 4 (For all systems): Type in the code string manually using the information on your screen or printed page.

   When you have successfully entered the code, touch or click the forward arrow at the bottom of the screen to continue. The Applying Xpert Check code screen will appear. See Figure 2-45.

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Xpert Check Code File

Here is the Xpert Check code for the recent data collection of your modules for the system identified below.

Xpert Check data collection performed on 30 September 2020 15:02:31 PST

GX Instrument Name:	My GeneXpert
Cepheid System ID:	123456
Software Version:	Xh1.5
Data Collected By:	admin1
Institution Name:	Institution1
Laboratory Name:	Lab1
Street Address:	100 Main Street, Suite 202
City:	New York
State/Province:	NY
Postal Code:	10001
Country:	USA
Email:	user@institution.com
Facility Phone Number:	408 400-0000
Extension:	
Mobile:	
ASP Code:	US01

Scan or enter the Xpert Check code to complete the Xpert Check process.

1. Cepheid recommends that system performance should be evaluated annually using Xpert Check.

2. Cepheid declares that the I-CORE modules in the GeneXpert® Instrument were checked using an Xpert Check product. NIST traceable qualification standards are used to control the parameters for the fluorescence standards of concentration, brightness, and spectrum. Cepheid products are manufactured, quantified and controlled under a Quality System compliant with ISO 13485 and QSR requirements.

GeneXpert® Xpert Check Version: Xh1.5

Page 1 of 1

Figure 2-44. Xpert Check Code File - Example

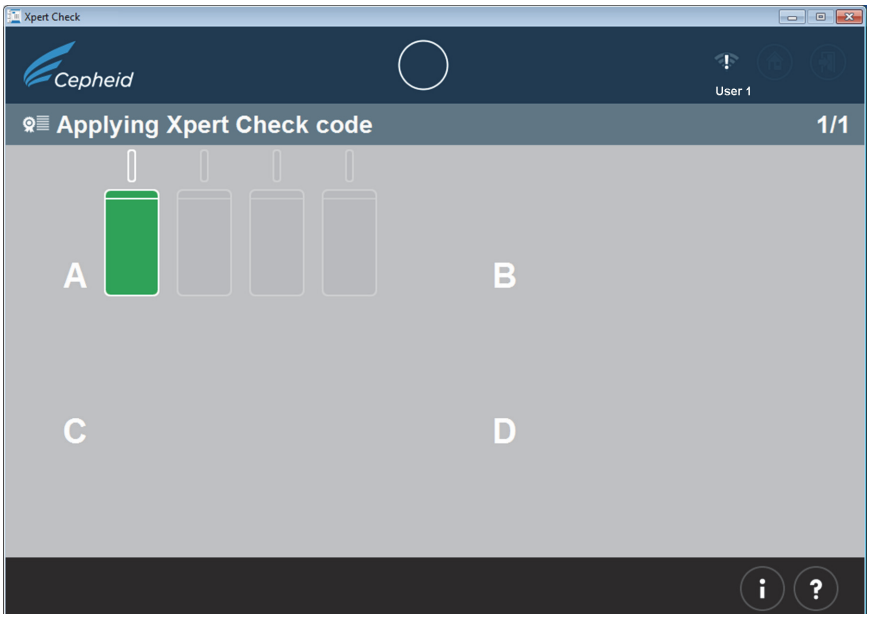

Figure 2-45. Applying Xpert Check code Screen Example

E. After the Xpert Check code has been applied, the Xpert Check Complete screen will appear with the location of the Xpert Check Report displayed in the **Xpert Check Data Directory** area. Write down the file path and location of the Xpert Check Report file, as shown. See Figure 2-46.

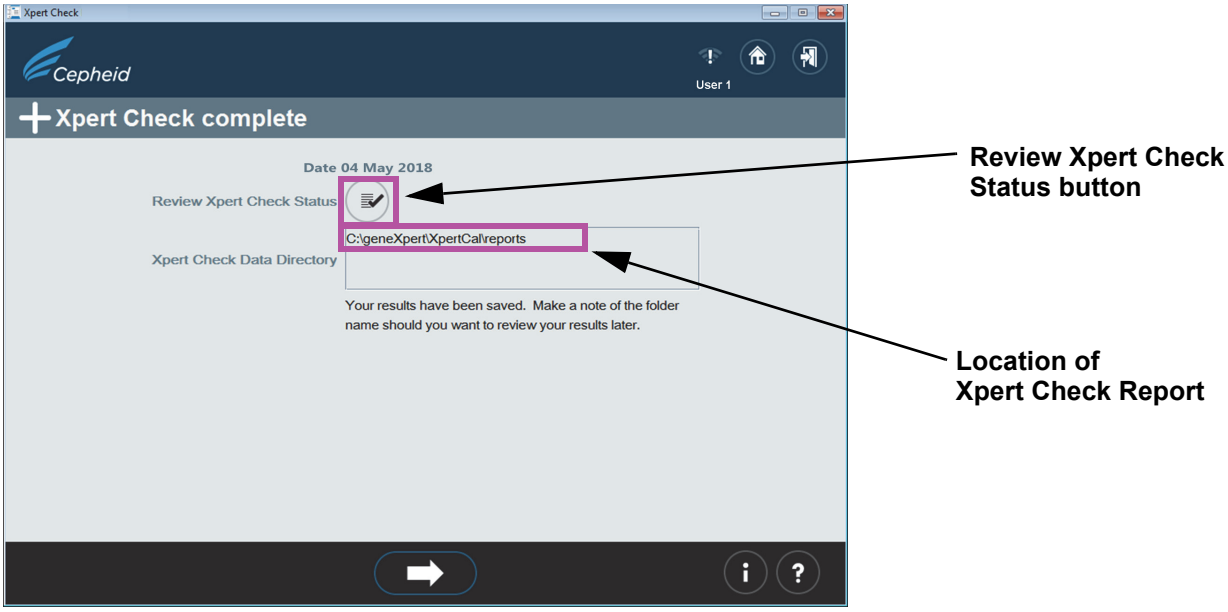

Figure 2-46. Xpert Check complete Screen

F. Touch or click the **Review Xpert Check Status** button (see Figure 2-46).

G. The Xpert Check status screen will appear. See Figure 2-47. In the Xpert Check status screen, the successfully checked modules are indicated by a **+** symbol on a green module.

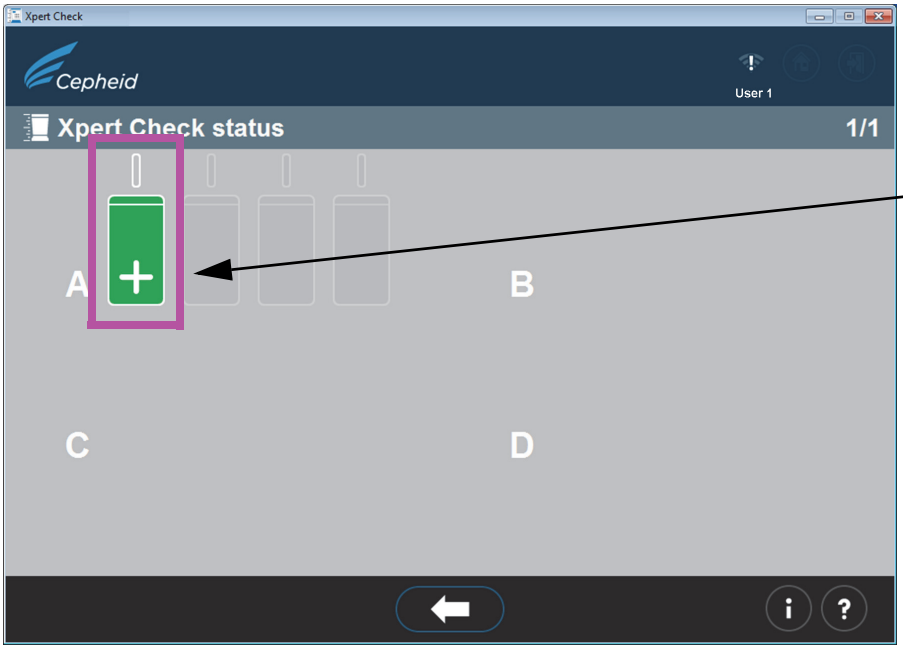

Figure 2-47. Xpert Check status Screen

Note

If the Xpert Check report on the computer has been deleted, contact your ASP or the local Cepheid Technical Support office for assistance.

7. Identify the generated Xpert Check Report file in the folder **C:\GeneXpert\XpertCal\Reports**.

8. Identify the generated Xpert Check Summary Report file in the folder **C:\GeneXpert\XpertCal\Reports**.

   A. See Figure 2-48 for an example of a Xpert Check Summary Report.

   The Xpert Check Summary Report lists the modules that had an unsuccessful test and require retesting or service.

   The modules requiring retesting or service are listed by serial number in Table 1 on the form in Figure 2-48. When requesting service, provide these listed serial numbers to your ASP or the local Cepheid Technical Support office.

   Gateway information is provided in Table 2 of the form.

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Xpert Check Summary Report

Please Note:

Xpert Check data collection performed on 30 September 2020 09:37:04 PDT
All modules that DID NOT pass Xpert Check are listed in Table 1: Modules Requiring Service.
Gateway Informations are provided in Table 2.
Complete test results for each module are listed in Table 3: Detailed Test Results by Module.

GX Instrument Name:	My 6Color
Instrument Serial Number:	12345
Data Collected By:	User1
Institution Name:	Institution1
Laboratory Name:	Laboratory Sunnyvale
Street Address:	123 Main Street
City:	Sunnyvale
State/Province:	CA
Postal Code:	90001
Country:	USA
Email:	User1@Institution1.com
Facility Phone Number:	408-400-XXXX
Extension:	
Mobile:	
ASP Code:	US03

Table 1: Modules Requiring Service

Module Serial Number / Location	Module Status
639563/A2	Skipped and Retest required
639565/A1	Requiring Service

Table 2: Gateway Information

Gateway Serial Number	MAC Address
804471	00:21:38:00:2E:1B
804470	00:21:38:00:2E:1A

GeneXpert® Xpert Check Version: Xh1.5 Page 1 of 2

Figure 2-48. Xpert Check Summary Report Example - Page 1

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Xpert Check Summary Report

Table 3: Detailed Test Results by Module Serial Number

The column header will show Module Serial Number, followed by (Location / Cartridge Lot).

If a module undergoes multiple tests, the Module Serial Number will be shown as Module Serial Number : Cartridge -Test Run.

Test	639565 (A1/00402)
Cartridge Load	pass
Module Tests	pass
Ambient Temperature	pass
Motherboard EEPROM	pass
ICORE EEPROM	pass
+12V Power Supply	pass
-12V Power Supply	pass
+24V Power Supply	pass
Valve Drive	pass
Valve Label Dropouts	pass
Valve Home Integrity	pass
Valve Timing	pass
Valve Drift	pass
Pump Drive	pass
Ultrasonic	pass
ICORE Heater	pass
ICORE Fan	pass
Force Sensor	pass
Optical Check	fail
EBF Value	pass
Probe Check	fail

1. Cepheid recommends that system performance should be evaluated annually using Xpert Check.

2. Cepheid declares that the I-CORE modules in the GeneXpert® Instrument were checked using an Xpert Check product. NIST traceable qualification standards are used to control the parameters for the fluorescence standards of concentration, brightness, and spectrum. Cepheid products are manufactured, quantified and controlled under a Quality System compliant with ISO 13485 and QSR requirements.

GeneXpert® Xpert Check Version: Xh1.5 Page 2 of 2

Figure 2-49. Xpert Check Summary Report Example - Page 2

2.4 Return System to Normal Operation

Note Return the system to normal operation by following one of the three procedures listed in this section for the GeneXpert Dx, GeneXpert Xpress, the GeneXpert Infinity 48s, or the GeneXpert Infinity-80.

2.4.1 GeneXpert Dx

Ensure all Xpert Check cartridges and CDs have been removed from the GeneXpert Dx.

1. Restart your GeneXpert system and computer. Follow the instructions in the GeneXpert Dx System Operator Manual.
2. The system will be ready for full operation.

2.4.2 GeneXpert Xpress

Ensure all Xpert Check cartridges and CDs have been removed from the GeneXpert Xpress.

1. Restart your GeneXpert Xpress system. Follow the instructions in the GeneXpert Xpress User's Guide.
2. The system will be ready for full operation

2.4.3 GeneXpert Infinity-48s or GeneXpert Infinity-80

Ensure all Xpert Check cartridges and CDs have been removed from the GeneXpert Infinity-48s or GeneXpert Infinity-80.

1. Restart the Xpertise software. Follow the instructions in the *GeneXpert Infinity System Operator Manual*.

The system will be in Automation mode, ready for full operation.

2.5 Information Key Screen

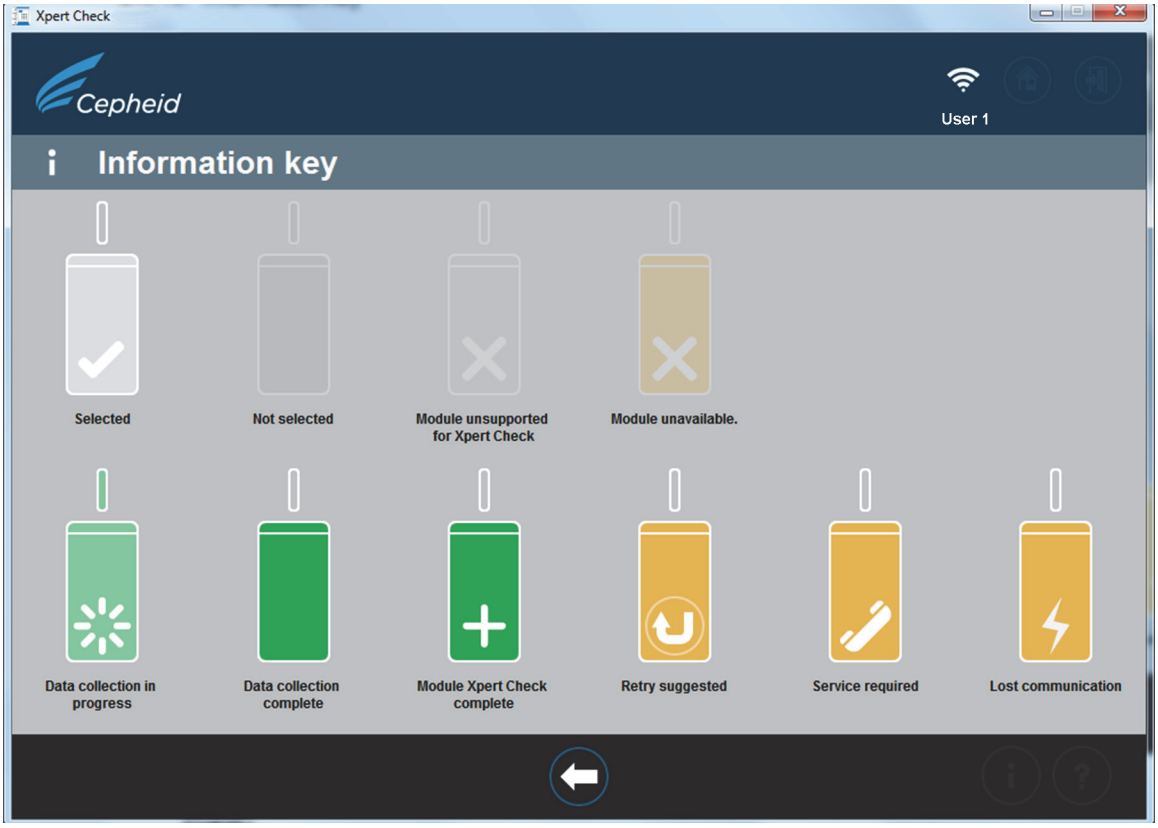

Figure 2-50. Information key Screen

2.5.1 Reasons to Repeat Xpert Check with a New Cartridge

If the onscreen instructions direct you to retest, repeat the test according to the instructions in Step B. on page 2-19.

2.5.2 Reasons to Repeat Xpert Check with the Same Cartridge

If software reports that the cartridge film seal was not broken, remove the original cartridge, rescan the cartridge barcode, open the lid, close the lid, and reinsert the cartridge. Restart the Xpert Check procedure for the affected module.

2.5.3 Application of Xpert Check Code

Xpert Check is not complete until the Cepheid-supplied Xpert Check code is applied to the system being tested. Upon receipt of the Quality Assurance Xpert Check Code from Cepheid, apply the code to your system using the Xpert Check Software to complete the Xpert Check process.

GeneXpert
Powered By CEPHEID INNOVATION

Xpert® HBV Viral Load

REF **GXHBV-VL-CE-10**

Инструкция по применению теста

CE 2797 **IVD**

Cepheid

Медицинское устройство для
диагностики *In Vitro*

301-5878-RU, Ред. F
2023-03

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Xpert® HBV Viral Load

Для диагностического применения *in vitro*.

1 Фирменное название

Xpert® HBV Viral Load

2 Наименование медицинского изделия

Xpert HBV VL

3 Целевое использование

Тест Cepheid Xpert® HBV Viral Load (VL) представляет собой тест *in vitro*, выполняемый методом амплификации нуклеиновых кислот для количественного определения ДНК вируса гепатита B (ВГВ) в образцах сыворотки или плазмы (с ЭДТА) человека, полученных у хронически ВГВ-инфицированных лиц, на автоматизированной системе GeneXpert®.

Тест предназначен для использования в контексте общей клинической картины и информации о прочих лабораторных маркерах прогноза заболевания, как вспомогательное средство оценки вирусологического ответа на противовирусную терапию путем определения изменений уровней ДНК ВГВ в плазме или сыворотке.

Тест не предназначен для скрининга на ВГВ доноров или для использования в качестве подтверждающего диагностического теста.

4 Краткие сведения и разъяснения

Вирус гепатита B (ВГВ) представляет собой небольшой ДНК-содержащий вирус с оболочкой из семейства Hepadnaviridae, который вызывает острый и хронический гепатит B. Он содержит небольшого размера геном из кольцевой ДНК диаметром 42 нм, двухцепочечной в одних частях и одноцепочечной в других. ВГВ содержит различные антигенные компоненты, включая поверхностный антиген вируса гепатита B (HBsAg), ядерный антиген вируса гепатита B (HBcAg) и е-антиген вируса гепатита B (HBeAg). ВГВ передается при попадании на кожу или слизистые оболочки крови или других биологических жидкостей инфицированного лица, от матери к новорожденному, при тесном бытовом контакте, при переливании крови без надлежащего скрининга или при повторном использовании нестерилизованных шприцев или игл для инъекций в медицинских учреждениях, при употреблении инъекционных наркотиков и половом контакте с инфицированным лицом.

Хронический вирусный гепатит B может быть HBeAg-положительным и HBeAg-отрицательным. Сераспространенность HBsAg в различных возрастных группах существенно различается в разных географических регионах. Самый высоким (> 5 %) этот показатель является в тропической Африке, в некоторых частях Балканского региона, в Восточной Азии, Океании и в бассейне реки Амазонки (Южная Америка). В Центральной Латинской Америке, Северной Америке и Западной Европе распространенность составляет менее 2 %. В целом почти половина населения земного шара проживает в высокоэндемичных регионах.[1] Заболеваемость хроническим гепатитом B и связанная с ним смертность связаны с персистенцией репликации вируса и развитием цирроза печени и (или) гепатоцеллюлярного рака.[2] Смертность от вирусного гепатита со временем увеличилась, и будет продолжать расти, если заболевшие лица не будут выявляться и получать лечение.[3]

Вакцина против ВГВ используется у новорожденных, и это позволило существенно уменьшить число новых случаев хронической инфекции, однако охват вакцинацией составляет всего 39 %.[3] В 2015 г. хроническая инфекция ВГВ имелась у 3,5 % населения планеты, при этом наибольшая встречаемость заболевания была характерна для Западно-Тихоокеанского региона и Африки.[3] Только 9 % инфицированных ВГВ знали о своем диагнозе, и только

8 % из осведомленных о диагнозе пациентов получали лечение.[3] Для лечения пациентов в соответствующих случаях применяются аналоги нуклеотидов и нуклеозидов, такие как тенофовир и энтекавир, так как они эффективно подавляют репликацию ВГВ, предотвращают прогрессирование до цирроза и уменьшают смертность, связанную с поражением печени.[1] Лечение ВГВ является пожизненным.[1]

5 Принципы проведения процедуры

Тест Xpert® HBV VL – это автоматический тест для количественного определения вируса гепатита B. Этот тест выполняют на анализаторах Cepheid GeneXpert и GeneXpert Infinity.

Система приборов GeneXpert автоматизирует и интегрирует процессы очистки образцов, амплификации нуклеиновых кислот и обнаружения целевой последовательности в простых или сложных образцах с использованием ПЦР в режиме реального времени. Система состоит из прибора, персонального компьютера и предустановленного программного обеспечения для выполнения тестов и просмотра результатов. Для работы с системой требуются одноразовые картриджи GeneXpert, которые содержат реагенты для ПЦР и в которых происходят очистка и процессы ПЦР. Поскольку картриджи представляют собой замкнутые системы, вероятность перекрестной контаминации между образцами сводится к минимуму. Полное описание систем представлено в соответствующем *руководстве оператора GeneXpert Dx* или *руководстве оператора GeneXpert Infinity*.

В комплект теста Xpert® HBV VL входят реагенты для обнаружения ДНК ВГВ в образцах и два внутренних контроля для количественного определения ДНК ВГВ. Внутренние контроли также предназначены для контроля правильности обработки целевой последовательности и для отслеживания присутствия ингибиторов ПЦР. Контроль зондов (Probe Check Control, PCC) предназначен для проверки регидратации реагентов, заполнения пробирки для ПЦР в картридже, целостности зондов и стабильности красителя.

Этот тест стандартизован по 4-му международному стандарту Всемирной организации здравоохранения (ВОЗ) для ДНК ВГВ для методик амплификации нуклеиновых кислот (код NIBSC: 10/266).[4]

6 Реагенты и приборы

6.1 Комплект поставки

Набор реагентов теста Xpert HBV VL содержит реагенты в количестве, достаточном для анализа 10 образцов и (или) образцов контроля качества. В набор входят:

Картриджи HBV VL со встроенными реакционными пробирками	**10**
	по 1 каждого типа в одном картридже
• Гранулы 1, 2 и 3 (лиофилизированные)	1,7 мл в одном картридже
• Реагент для лизирования (гуанидина тиоцианат)	0,5 мл в каждом картридже
• Ополаскивающий реагент	1,5 мл в каждом картридже
• Элюирующий реагент	1,5 мл в каждом картридже
• Реагент связывания	0,48 мл в каждом картридже
• Реагент протеиназа K	
Одноразовые пипетки для переноса, 1 мл	**10 в каждом наборе**
Компакт-диск	**1 в каждом наборе**
• Файл описания теста (ADF)	
• Инструкцию по импортированию файла ADF в программное обеспечение GeneXpert и Infinity	
• Инструкция по применению (вкладыш-инструкция)	

Прим. Паспорта безопасности вещества (Safety Data Sheet, SDS) можно найти по ссылкам www.cepheid.com или www.cepheidinternational.com на вкладке **ПОДДЕРЖКА** (SUPPORT).

Прим. Для изготовления бычьего сывороточного альбумина (БСА), входящего в состав гранул данного изделия, использовалась только плазма бычьей крови животных, выращенных в США. В пищу быков не добавлялись белки, полученные из тканей жвачных животных, а также другие белки животного происхождения; всех животных обследовали до и после забоя. Во время производства не происходило смешивания сырья с другими материалами животного происхождения.

7 Хранение и обращение

- Храните картриджи анализа Xpert® HBV VL при температуре 2–35 °C до истечения срока годности, указанного на этикетке.
- Если картриджи хранятся на холоде, доведите их до комнатной температуры перед применением.
- Не используйте картриджи с истекшим сроком годности.
- Не открывайте крышку картриджа до тех пор, пока не будете готовы начать выполнение теста.
- Не используйте картриджи с признаками утечки.

8 Необходимые материалы, не входящие в комплект поставки

- Анализатор GeneXpert® Dx или GeneXpert® Infinity (номер по каталогу зависит от конфигурации): прибор GeneXpert, компьютер с патентованным программным обеспечением GeneXpert версии 4.7b или выше (системы GeneXpert Dx) либо Xpertise версии 6.4b или выше (системы Infinity-80/Infinity-48s), сканер штрих-кодов и соответствующее руководство оператора прибора GeneXpert.
- Принтер: если необходим принтер, обратитесь в службу технической поддержки компании Cepheid, чтобы организовать приобретение рекомендованного принтера.
- Отбеливатель или гипохлорит натрия
- Денатурированный этанол

9 Предупреждения и меры предосторожности

9.1 Общие положения

- Для использования при проведении диагностических тестов *in vitro*.
- При работе со всеми биологическими образцами, в том числе и с использованными картриджами, следует считать их способными к переносу возбудителей инфекционных заболеваний. Поскольку часто невозможно предугадать, что может переносить инфекцию, обращение со всеми биологическими образцами требует соблюдения стандартных мер предосторожности. Методические рекомендации по обращению с образцами предоставляются агентством «Центры по контролю и профилактике заболеваний США» (U.S. Centers for Disease Control and Prevention)[5] и Институтом клинических и лабораторных стандартов (Clinical and Laboratory Standards Institute).[6]
- С целью избежать контаминации образцов и реагентов рекомендуется следовать принципам надлежащей лабораторной практики, включая правило замены перчаток перед началом работы с образцом следующего пациента.
- Следуйте принятым в учреждении процедурам техники безопасности по работе с химическими веществами и обращению с биологическими образцами.
- Не заменяйте реагенты теста Xpert HBV VL другими реагентами.
- Не открывайте крышку картриджа Xpert HBV VL до тех пор, пока не будете готовы внести образец.
- Не используйте картридж, если он упал после извлечения из упаковки.
- Не встряхивайте картридж. Встряхивание или падение картриджа после вскрытия его крышки может привести к получению недействительных результатов.
- Не используйте картридж с поврежденной реакционной пробиркой.
- Не закрывайте этикетку со штрих-кодом на картридже.

- При помощи пипетки для переноса или прецизионной пипетки внесите образец в картридж. Не переливайте образец в картридж непосредственно из устройства для сбора.
- Каждый одноразовый картридж Xpert HBV VL применяется для проведения только одного теста. Не используйте картриджи повторно.
- Каждая одноразовая пипетка используется для переноса одного образца. Не используйте одноразовые пипетки повторно.
- Пользуйтесь чистым лабораторным халатом и перчатками. Перчатки подлежат замене перед обработкой каждого следующего образца.
- В случае загрязнения рабочей зоны или оборудования образцами или контролями тщательно протрите контаминированный участок свежеприготовленным 0,5 % раствором гипохлорита натрия (или разбавленным в соотношении 1:10 хлорсодержащим хозяйственным отбеливателем). Затем протрите поверхность 70 % этиловым спиртом. Перед продолжением работы дайте рабочим поверхностям полностью высохнуть.
- Биологические образцы, устройства для переноса и использованные картриджи следует считать возможными переносчиками возбудителей инфекционных заболеваний, при обращении с ними необходимо соблюдать стандартные меры предосторожности. Для правильного удаления в отходы использованных картриджей и неиспользованных реагентов следуйте принятым в вашем учреждении правилам защиты окружающей среды при обращении с отходами. Эти материалы могут иметь свойства химически опасных отходов и требовать выполнения особых национальных или региональных процедур удаления в отходы. Если принятые в стране или регионе правила не дают ясных указаний по правильному удалению в отходы, биологические образцы и использованные картриджи следует удалять в отходы с соблюдением правил ВОЗ (Всемирной организации здравоохранения) относительно обращения с медицинскими отходами и их удаления.[7]

10 Опасные химические факторы[8,9]

Реагент для лизирования (гуанидина тиоцианат)

- Сигнальное слово: ПРЕДОСТЕРЕЖЕНИЕ
- **Заявления об опасности СГС ООН**
  - Вредно при проглатывании
  - Вызывает слабое раздражение кожи
  - Вызывает раздражение глаз
- **Предостерегающие заявления СГС ООН**
  - **Профилактика**
    - После использования тщательно вымыть.
  - **Реагирование**
    - При раздражении кожи: Обратиться за медицинской консультацией/помощью.
    - ПРИ ПОПАДАНИИ В ГЛАЗА: Осторожно промыть водой в течение нескольких минут. Снять контактные линзы, если вы ими пользуетесь, и если это легко сделать. Продолжить промывание.
    - Если раздражение глаз не проходит: Обратиться за медицинской консультацией/помощью.
    - При плохом самочувствии обратиться в ТОКСИКОЛОГИЧЕСКИЙ ЦЕНТР или к врачу-специалисту/терапевту.

11 Образцы: взятие, транспортировка и хранение

Цельную кровь следует собирать в пробирки для сбора образцов с K_2-ЭДТА, пробирки PPT-ЭДТА или пробирки для сбора сыворотки, и центрифугировать для отделения плазмы/сыворотки от эритроцитов, в соответствии с инструкциями изготовителя.

- Для теста Xpert HBV VL требуется не менее 0,6 мл плазмы или сыворотки. Если используется пипетка для переноса, входящая в набор, ее следует заполнить сывороткой или плазмой до четвертой метки (1,0 мл). Либо, при использовании прецизионной пипетки, требуется 0,6 мл плазмы или сыворотки. См. указания в Раздел 12.2, вариант 1 и вариант 2, соответственно.
- Перед получением плазмы или сыворотки цельную кровь можно хранить до 24 часов при температуре 2–35 °C или до 3 дней при температуре 2–8 °C. Центрифугировать в соответствии с инструкциями изготовителя.
- После центрифугирования и отделения плазму и сыворотку можно хранить до исследования в течение до 24 часов при температуре 2–35 °C или до 7 дней при температуре 2–8 °C.

- Стабильность замороженных (от -80 °C до -20 °C) образцов плазмы и сыворотки сохраняется в течение 6 недель.
- Стабильность образцов плазмы и сыворотки сохраняется в течение не более трех циклов замораживания/размораживания.
- До переноса в картридж образцы плазмы и сыворотки следует разморозить и дождаться их согревания до комнатной температуры.
- При транспортировке образцов цельной крови, плазмы и сыворотки следует соблюдать местные, региональные и федеральные нормативные требования по транспортировке возбудителей.

12 Процедура

12.1 Подготовка образца

Прим. Анализ следует начать не позднее чем через 4 часа после того, как образец был помещен в картридж.

1. После центрифугирования образца цельной крови, плазму можно перенести при помощи пипетки непосредственно в картридж. Для получения действительных результатов крайне важно использовать достаточный объем образца (см. указания в Раздел 12.2. Подготовка картриджа).
2. Замороженные образцы перед использованием следует поместить в условия комнатной температуры (20–35 °C) до их полного оттаивания и согревания до комнатной температуры.
3. Образцы плазмы и сыворотки, хранившиеся при температуре 2–8 °C, перед использованием необходимо извлечь из холодильника и дождаться их согревания до комнатной температуры.
4. Образцы плазмы, хранившиеся при температуре 2–8 °C или замороженные и оттаявшие, перед использованием необходимо перемешать на вихревой мешалке в течение 10 секунд. Мутный образец следует осветлить непродолжительным центрифугированием.

12.2 Подготовка картриджа

1. Пользуйтесь одноразовыми защитными перчатками.
2. Если картриджи хранятся на холоде, доведите их до комнатной температуры перед применением.
3. Осмотрите картридж на предмет отсутствия повреждений. В случае повреждения не используйте его.
4. Нанесите на картридж этикетку с идентификатором образца.
5. Откройте крышку картриджа.
6. Внесите образец в картридж.
   - **Способ 1.** Если используется пипетка для переноса, входящая в набор (см. Рисунок 1), ее следует заполнить плазмой или сывороткой (из пробирки для сбора) до четвертой метки (1,0 мл) или несколько выше. Выпустите содержимое пипетки в предназначенную для образца камеру картриджа (см. Рисунок 2).
   - **Способ 2.** При использовании прецизионной пипетки, необходимо перенести 0,6 мл плазмы или сыворотки (из пробирки для сбора) в предназначенную для образца камеру картриджа (см. Рисунок 2).

Прим. Не снимайте тонкую полимерную пленку, покрывающую внутреннее кольцо с 13 портами картриджа.

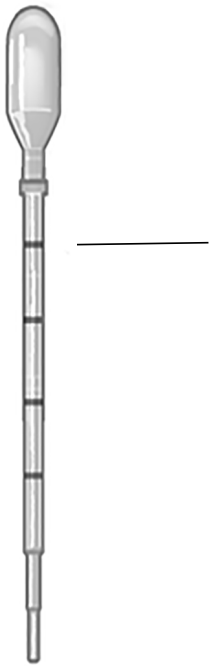

Рисунок 1. Пипетка для переноса теста Xpert HBV VL

7. Закройте крышку картриджа. Убедитесь, что крышка надежно защелкнулась на месте.

Рисунок 2. Картридж Xpert Xpert HBV VL (вид сверху)

12.3 Запуск теста

Важное замечание **Прежде чем начинать анализ, убедитесь, что файл с описанием теста (assay definition file, ADF) Xpert HBV VL импортирован в программное обеспечение.**

В данном разделе перечислены основные действия при выполнении теста. Подробные инструкции приводятся в *руководстве оператора системы GeneXpert Dx* или *руководстве оператора системы GeneXpert Infinity*, в зависимости от используемой модели прибора.

Прим. Выполняемые действия могут быть другими, если системный администратор изменит установленную по умолчанию рабочую последовательность системы.

1. Включите приборную систему GeneXpert:

- При использовании GeneXpert Dx вначале следует включить прибор, а затем компьютер. Программное обеспечение GeneXpert Dx запустится автоматически, или же может потребоваться двойной щелчок по ярлыку программного обеспечения GeneXpert Dx на рабочем столе Windows®.

  или

- При использовании прибора GeneXpert Infinity следует включить прибор. Программное обеспечение GeneXpert запустится автоматически либо после двойного щелчка на ярлыке программного обеспечения Xpertise, находящегося на рабочем столе Windows®.

2. Войдите в программное обеспечение приборной системы GeneXpert, используя свое имя пользователя и пароль.
3. В окне системы GeneXpert выберите пункт **Создать анализ (Create Test)** (для GeneXpert Dx) или выберите пункт **Команды (Orders)**, а затем **Задать команду на проведение анализа (Order Test)** (для Infinity). Откроется окно **Создать анализ (Create Test)**.
4. Отсканируйте «ID пациента» (Patient ID) (не обязательно). Если вводится «ID пациента» (Patient ID), то проследите за тем, чтобы он был введен корректно. «ID пациента» (Patient ID) указывается в левой части окна «Просмотреть результаты» (View Results) и связывается с результатами теста.
5. Отсканируйте «ID образца» (Sample ID) или введите вручную «ID образца» (Sample ID). Если вводится «ID образца» (Sample ID), проследите за тем, чтобы он был введен корректно. «ID образца» (Sample ID) указывается в левой части окна «Просмотреть результаты» (View Results) и связывается с результатами анализа.
6. Отсканируйте штрихкод на картридже теста Xpert HBV VL. На основе информации, считанной со штрихкода, программным обеспечением автоматически заполняются следующие поля: «ID партии реагента» (Reagent Lot ID), «С/Н картриджа» (Cartridge SN) и «Срок годности» (Expiration Date).

Прим. Если штрихкод картриджа Xpert HBV VL не сканируется, повторите анализ с новым картриджем.

7. Щелкните **Начать анализ (Start Test)** (для GeneXpert Dx) или **Отправить (Submit)** (для Infinity). В появившемся диалоговом окне введите свой пароль.
8. При использовании системы GeneXpert Infinity поместите картридж на конвейерную ленту. Загрузка картриджа произойдет автоматически, будет выполнен тест, а использованный картридж будет удален в контейнер для отходов.

   или

   Для прибора GeneXpert Dx:

   a) Откройте дверцу модуля прибора с мигающим зеленым индикатором и загрузите картридж.
   b) Закройте дверцу. После этого начинается тест, и зеленая индикаторная лампа перестает мигать. По завершении процесса теста индикаторная лампа выключается.
   c) Перед открытием дверцы модуля и извлечением картриджа дождитесь разблокирования системой замка дверцы.
   d) Удалите использованные картриджи в подходящий контейнер для сбора отходов образцов согласно стандартной практике, принятой в вашем учреждении.

13 Просмотр и печать результатов

В данном разделе перечислены основные действия по просмотру и печати результатов. Более подробные инструкции по просмотру и печати результатов см. в *руководстве оператора системы GeneXpert Dx* или *руководстве оператора системы GeneXpert Infinity*, в зависимости от используемого прибора.

1. Для просмотра результатов выберите ярлык **Просмотреть результаты (View Results).**
2. По завершении теста нажмите кнопку **Отчет (Report)** в окне **Просмотреть результаты (View Results)** для просмотра и (или) получения отчета в формате PDF.

14 Контроль качества

Каждый тест содержит контроль достаточности объема образца (Sample Volume Adequacy, SVA), внутренние количественные стандарты (Internal Quantitative Standard, IQS) высокой и низкой концентрации (IQS-H и IQS-L), а также специальные параметры партии (Lot Specific Parameters, LSP) и контроль зондов (Probe Check Control, PCC).

- **Контроль достаточности объема образца (SVA)** — предназначен для подтверждения правильности внесения образца в картридж. Контроль SVA позволяет подтвердить, что в камеру для образца внесен надлежащий объем

образца. Контроль SVA считается пройденным, если его результат соответствует валидированным критериям приемлемости. Если контроль SVA не пройден, отображается либо сообщение **Ошибка 2096 (Error 2096)**, если образец не был внесен в картридж, либо сообщение **ОШИБКА 2097 (ERROR 2097)**, если в картридж был внесен недостаточный объем образца. Система не позволит пользователю возобновить тестирование.

- **Внутренние количественные стандарты высокой и низкой концентрации (IQS-H и IQS-L)** — это две линеаризованные плазмиды, последовательность которых не связана с последовательностью ВГВ. Они находятся в каждом картридже и проходят через весь процесс анализа. Эти стандарты используют для расчета концентрации ДНК ВГВ в образце. Кроме того, IQS-H и IQS-L обнаруживают связанное с образцом ингибирование реакции ПЦР в реальном времени, выполняя функцию контролей обработки образца. Контроли IQS-H и IQS-L считаются пройденными, если их результаты соответствуют валидированным критериям приемлемости.
- **Параметры, специфичные для партии (Lot Specific Parameters, LSP), для количественного определения** — каждая партия набора содержит характерные для нее LSP, созданные путем анализа калибровочной панели ВГВ, прослеживаемой до 4-го международного стандарта ВОЗ для ВГВ (код NIBSC: 10/266)[4], и IQS-H и IQS-L. Эти LSP уникальны для каждой партии реагента и используются для обеспечения правильного количественного определения.
- **Контроль зондов (Probe Check Control, PCC)** — перед запуском ПЦР анализатор GeneXpert измеряет флуоресцентный сигнал от зондов для отслеживания регидратации гранул, заполнения реакционной пробирки, целостности зондов и стабильности красителя. Контроль PCC считается пройденным, если флуоресцентные сигналы соответствуют валидированным критериям приемлемости.
- **Внешние контроли** — в соответствии с принципами надлежащей лабораторной практики, внешние контроли, не входящие в данный набор, следует использовать согласно применимым требованиям местных и государственных уполномоченных организаций.

15 Интерпретация результатов

Результаты интерпретируются системой приборов GeneXpert на основании измерений флуоресцентных сигналов и встроенных алгоритмов расчета; они отображаются в окне «Просмотреть результаты» (View Results) (см. Рисунок 3 — Рисунок 8). Возможные результаты показаны в Таблица 1.

Таблица 1. Результаты теста Xpert HBV VL и их интерпретация

Результат	Интерпретация
ВГВ обнаружен, МЕ/мл (log X,XX) (HBV DETECTED IU/mL, log X.XX) См. Рисунок 3.	ДНК ВГВ обнаружена в концентрации XX МЕ/мл (log X,XX). ● Титр ДНК ВГВ находится в пределах диапазона количественного определения теста (10–1,00E09 МЕ/мл). ● IQS-H и IQS-L: ПРОЙДЕН (PASS). ● Контроль зондов — ПРОЙДЕН (PASS); все проверки в рамках контроля зондов успешно пройдены.
ВГВ ОБНАРУЖЕН >1,00E09 МЕ/мл (HBV DETECTED >1.00E09 IU/mL) См. Рисунок 4.	Обнаруженный титр ДНК ВГВ выше границы диапазона количественного определения теста. ● IQS-H и IQS-L: ПРОЙДЕН (PASS). ● Контроль зондов — ПРОЙДЕН (PASS); все проверки в рамках контроля зондов успешно пройдены.
ВГВ ОБНАРУЖЕН <10 МЕ/мл (HBV DETECTED <10 IU/mL) См. Рисунок 5.	Обнаруженный титр ДНК ВГВ ниже границы диапазона количественного определения теста. ● IQS-H и IQS-L: ПРОЙДЕН (PASS). ● Контроль зондов — ПРОЙДЕН (PASS); все проверки в рамках контроля зондов успешно пройдены.
ВГВ НЕ ОБНАРУЖЕН (HBV NOT DETECTED) См. Рисунок 6.	ДНК ВГВ не обнаружена. ● IQS-H и IQS-L: ПРОЙДЕН (PASS). ● Контроль зондов — ПРОЙДЕН (PASS); все проверки в рамках контроля зондов успешно пройдены.

Результат	Интерпретация
НЕДЕЙСТВИТЕЛЬНЫЙ (INVALID) См. Рисунок 7.	Невозможно установить, присутствует или отсутствует в образце ДНК ВГВ. Повторите тест согласно инструкциям, содержащимся в Раздел 16.2. Процедура повторного теста. • IQS-H и (или) IQS-L: НЕ ПРОЙДЕН (FAIL); пороги цикла (Ct) не находятся в действительном диапазоне. • Контроль зондов — ПРОЙДЕН (PASS); все проверки в рамках контроля зондов успешно пройдены.
ОШИБКА (ERROR) См. Рисунок 8.	Невозможно установить, присутствует или отсутствует в образце ДНК ВГВ. Повторите тест согласно инструкциям, содержащимся в Раздел 16.2. Процедура повторного теста. • Контроль зондов — НЕ ПРОЙДЕН (FAIL)*; все или один из контролей зондов не пройдены. Если контроль зондов пройден, ошибка вызвана выходом за границы действительного диапазона предельного максимального давления или сбоем компонента системы.
НЕТ РЕЗУЛЬТАТА (NO RESULT)	Невозможно установить наличие или отсутствие ДНК ВГВ. Повторите тест согласно инструкциям, содержащимся в Раздел 16.2. Процедура повторного теста. Сообщение **НЕТ РЕЗУЛЬТАТА (NO RESULT)** свидетельствует о том, что собрано недостаточно данных. Такое сообщение, например, может появляться, если лаборант прервал текущий процесс анализа.

Прим. Снимки с экранов тестов даны только в качестве примеров. Номер версии может отличаться от показанной на снимках с экрана в этой инструкции по применению.

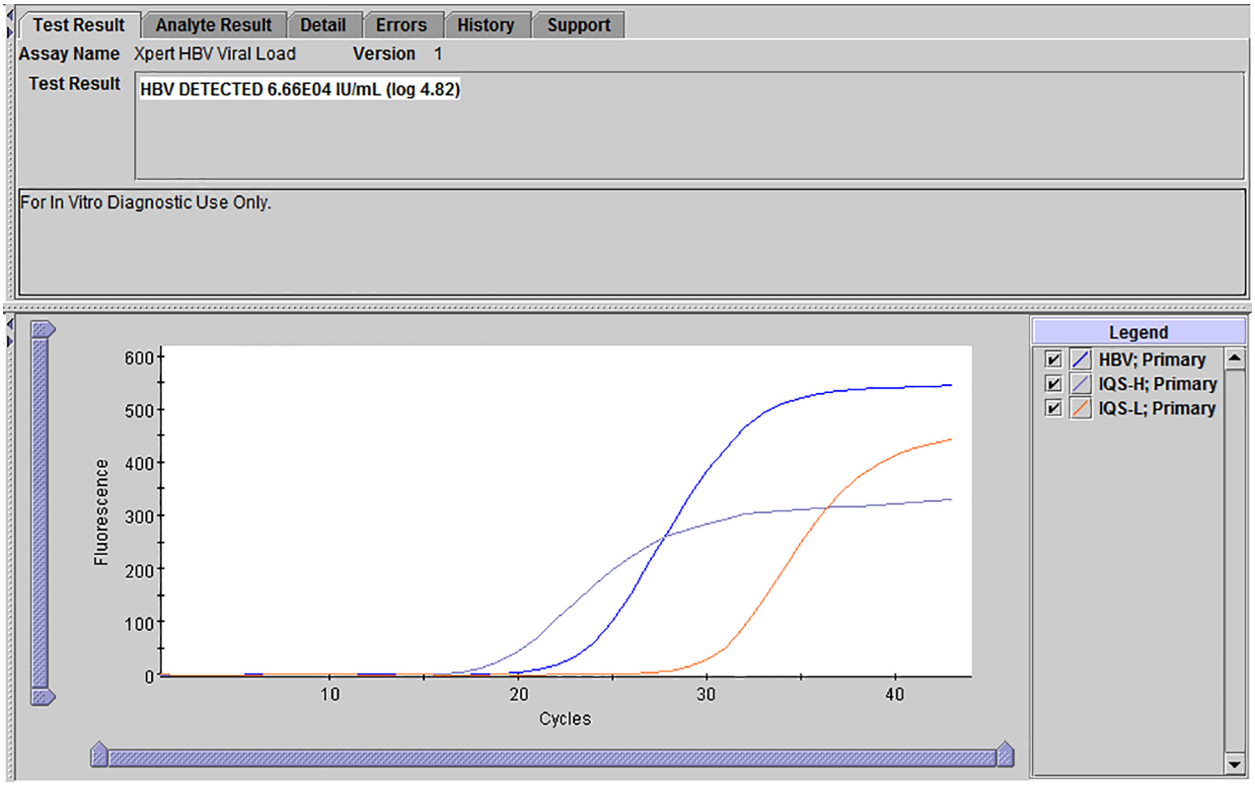

Рисунок 3. Результат: ВГВ обнаружен и количественно определен

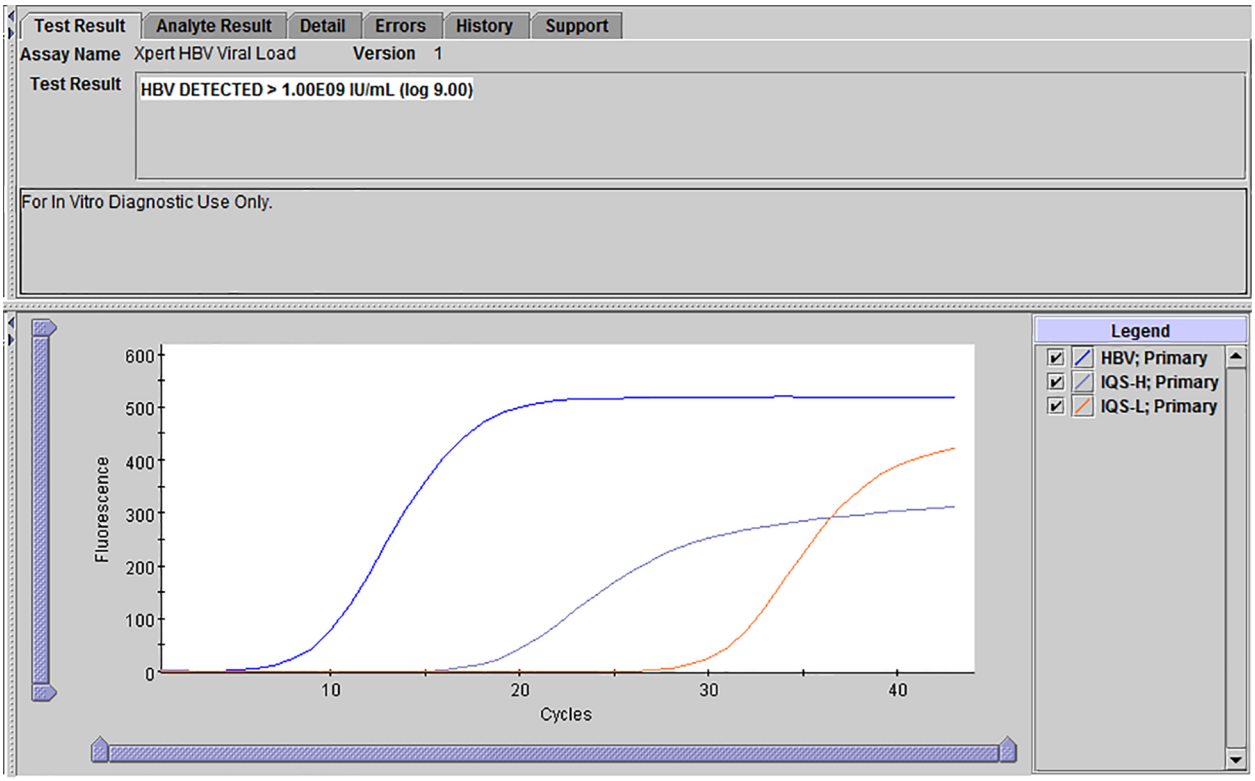

Рисунок 4. Результат: ВГВ обнаружен, но его титр выше границы диапазона количественного определения теста

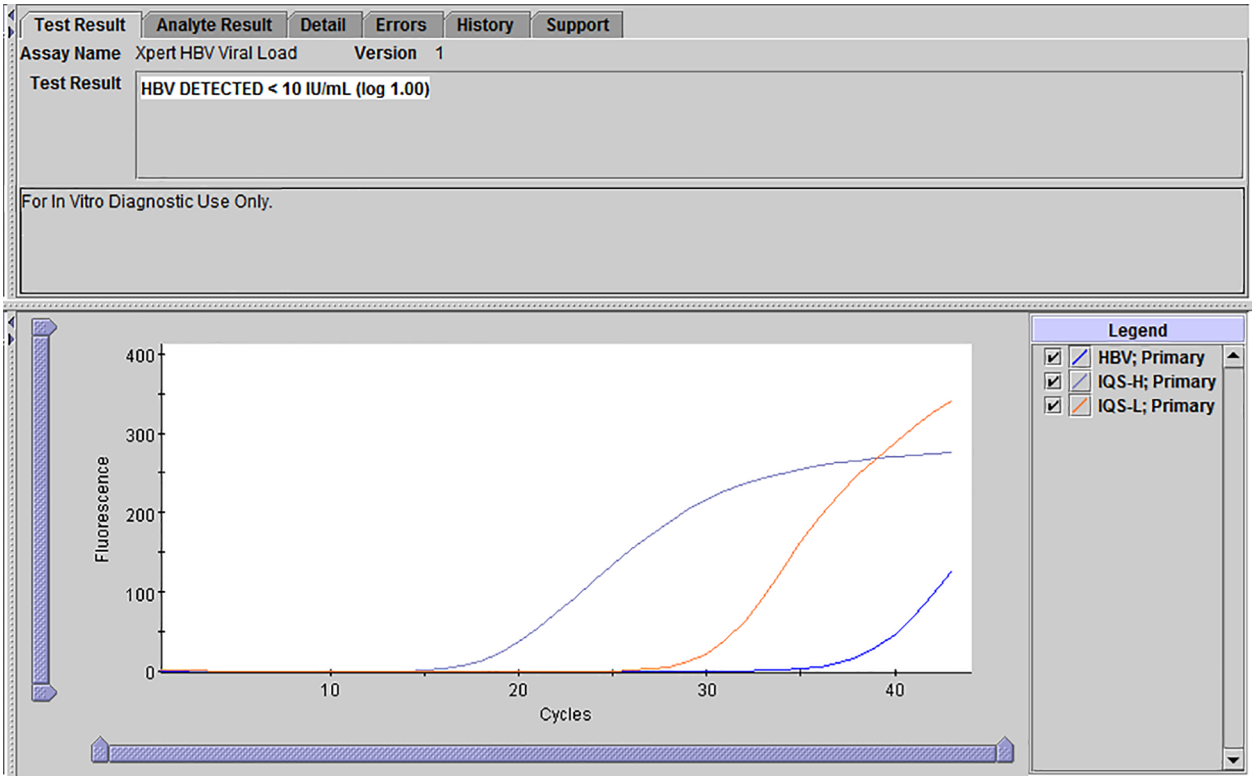

Рисунок 5. Результат: ВГВ обнаружен, но его титр ниже границы диапазона количественного определения теста

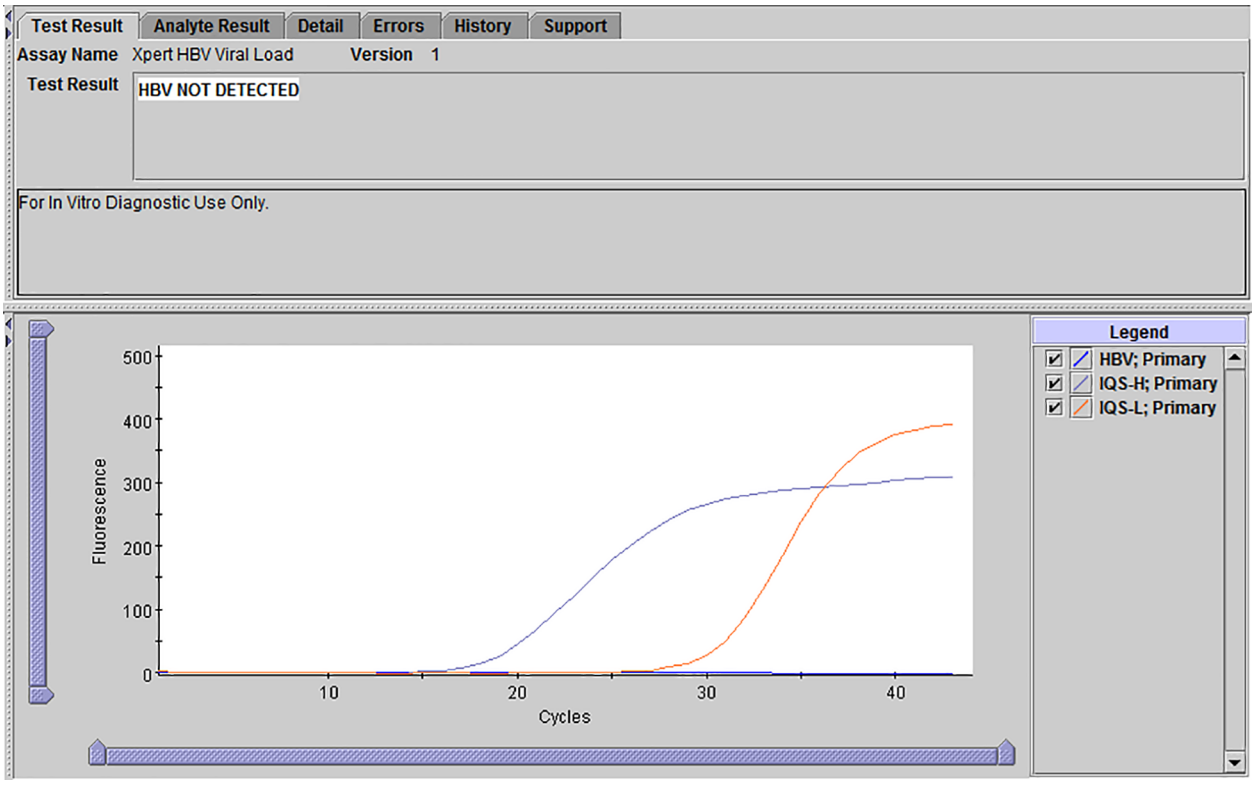

Рисунок 6. Результат: ВГВ не обнаружен

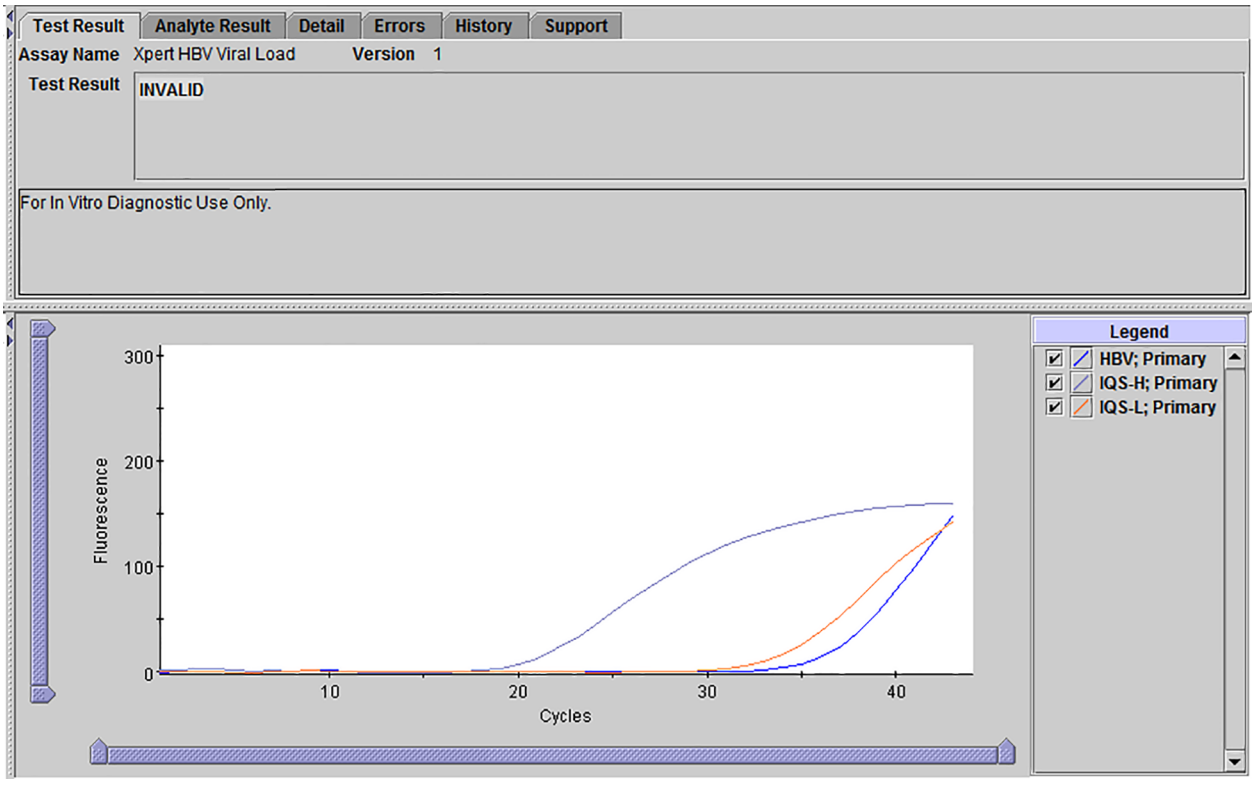

Рисунок 7. Результат: Недействительный результат

Рисунок 8. Результат: Ошибка

16 Повторное выполнение теста

16.1 Причины повторного выполнения теста

При получении любого из следующих результатов теста повторите тест в соответствии с указаниями, изложенными в Раздел 16.2. Процедура повторного теста.

- **НЕДЕЙСТВИТЕЛЬНЫЙ (INVALID)** результат может быть связан с одной или более следующих причин:
  - Значения Ct IQS-H и (или) IQS-L не находятся в действительном диапазоне.
  - Образец не был обработан надлежащим образом, или произошло ингибирование ПЦР.
- Результат **ОШИБКА (ERROR)** показывает, что тест был прерван. Возможные причины: внесен недостаточный объем образца, неправильное заполнение реакционной пробирки, обнаружена проблема целостности зонда реагента или превышен максимальный предел давления.
- Сообщение **НЕТ РЕЗУЛЬТАТА (NO RESULT)** свидетельствует о том, что собрано недостаточно данных. Например, если оператор прервал выполняющийся процесс анализа или произошел перебой в подаче электроэнергии.

16.2 Процедура повторного теста

При получении результата **НЕДЕЙСТВИТЕЛЬНЫЙ (INVALID)**, **ОШИБКА (ERROR)** или **НЕТ РЕЗУЛЬТАТА (NO RESULT)** выполните повторное тестирование соответствующего образца с использованием нового картриджа (не допускайте повторного использования картриджа).

1. Извлеките новый картридж из набора.
2. Выполните действия, указанные в Раздел 12. Процедура, включая Раздел 12.2. Подготовка картриджа и Раздел 12.3. Запуск теста.

17 Ограничения

- Во избежание контаминации образцов и реагентов рекомендуется следовать принципам надлежащей лабораторной практики, включая правило замены перчаток перед началом работы с каждым следующим образцом.
- Редкие мутации в целевом регионе теста Xpert HBV VL могут влиять на связывание праймера или зонда, в результате чего концентрация окажется заниженной или вирус не обнаружится.
- Данный тест был валидирован только для использования с образцами сыворотки и плазмы с ЭДТА. Тестирование других типов образцов может привести к получению неточных результатов.
- Отрицательные результаты теста не исключают наличия инфекции ВГВ. Поэтому тест Xpert HBV VL не следует использовать в качестве диагностического для подтверждения инфицирования ВГВ.

18 Функциональные характеристики

18.1 Порог обнаружения

Порог обнаружения теста Xpert HBV VL был определен для генотипа A вируса гепатита B путем тестирования серийных разведений 4-го международного стандарта ВОЗ для ДНК вируса гепатита B (код NIBSC 10/266),[4] разведенного в сыворотке и плазме с ЭДТА, отрицательных на ВГВ. Панели из образцов сыворотки или плазмы с ЭДТА шести уровней концентрации и отрицательного образца тестировали, соответственно, с использованием реагентов четырех или трех партий. Каждый компонент панели тестировали в течение трех дней, 24 повтора на партию реагентов. Всего каждый компонент панели образцов плазмы был исследован в 96 повторах, а панели образцов сыворотки — в 72 повторах.

Результаты для образцов сыворотки и плазмы с ЭДТА представлены в Таблица 2. Исследование показало, что тест Xpert HBV VL позволяет обнаруживать ДНК ВГВ в международном стандарте ВОЗ в концентрации 3,20 МЕ/мл при исследовании плазмы с ЭДТА и в концентрации 5,99 МЕ/мл при исследовании сыворотки с долей положительных результатов 95% по результатам регрессионного пробит-анализа.

Таблица 2. Порог обнаружения теста Xpert HBV VL при использовании 4-го международного стандарта ВОЗ для ВГВ

Генотип	Материал	Номинальная концентрация ВГВ (МЕ/мл)	Количество действительных повторов	Количество положительных результатов	Доля положительных результатов (%)	95 % LOD по пробит-анализу (95 % доверительный интервал)
A	Плазма	10	95	95	100	3,20 МЕ/мл (2,79–3,60 МЕ/мл)
		5	96	94	98	
		2,5	96	82	85	
		1,25	96	62	65	
		0,625	96	41	43	
		0	96	0	0	
A	Сыворотка	10	72	70	97	5,99 МЕ/мл (5,13–6,86 МЕ/мл)
		5	72	63	88	
		2,5	72	58	81	
		1,25	72	37	51	
		0,625	71	15	21	
		0	72	0	0	

Порог обнаружения для генотипов ВГВ от B до H определяли путем тестирования панелей из шести или семи компонентов, приготовленных путем внесения ВГВ-положительных образцов, представляющих каждый генотип (генотипы от B до G из международной референсной панели ВОЗ, код PEI: 5086/08, и генотипа H в клиническом образце) в плазму с ЭДТА, отрицательную на ВГВ. Каждый компонент панели тестировали в течение трех дней, с использованием трех партий реагентов, всего по 24 повтора на компонент. Результаты представлены в Таблица 3.

Таблица 3. Порог обнаружения для ВГВ генотипов от B до H в плазме с ЭДТА

Генотип	95 % LOD по пробит-анализу (МЕ/мл)	95 % доверительный интервал (МЕ/мл)
B	1,34	0,98–1,69
C	1,63	1,23–2,03
D	3,96	3,01–4,92
E	3,77	2,76–4,78
F	2,39	1,82–2,96
G	1,21	0,95–1,47
B	3,84	2,91–4,77

Порог обнаружения для ВГВ генотипов от B до H подтверждали в образцах сыворотки согласно стандарту CLSI EP17-A2[10] в 24 повторах. Если не удавалось достичь доли положительных результатов > 85 %, тестировали образцы более высоких концентраций. Результаты представлены в Таблица 4.

Таблица 4. Подтверждение порога обнаружения (LOD) для генотипов от B до H в сыворотке

Генотип	Номинальная концентрация ВГВ (МЕ/мл)	Доля положительных результатов (%)
B	1,34	88
C	3,25	96
D	3,96	96
E	3,77	96
F	2,39	92
G	1,21	88
B	3,84	100

Функциональные характеристики теста Xpert HBV VL также оценивали в отношении вируса гепатита B с мутацией в прекоровом участке. Для этого тестировали с одной партией реагентов секвенированный клинический образец ВГВ, включавший две мутации в прекоровом участке (C1858T и G1896A) и две мутации основного корового промотора (A1762T и G1764A), разведенный до концентрации 10 МЕ/мл в сыворотке и плазме с ЭДТА. Доля положительных результатов, равная 100 %, достигалась для всех 24 повторов для каждого материала.

18.2 Предел количественного определения

Нижний предел количественного определения (lower limit of quantitation LLOQ) — это наименьшая концентрация ДНК ВГВ, которая может быть количественно определена с приемлемой прецизионностью и правильностью, и устанавливаемая путем оценки общей аналитической ошибки (total analytical error, TAE) и подхода, основанного на разности двух измерений. LLOQ определяли с использованием четырех независимых образцов, представляющих генотипы ВГВ от A до D, в плазме с ЭДТА, при концентрации, близкой к порогу обнаружения теста. Каждый образец тестировали с четырьмя партиями реагентов, по 8–24 повтора на партию. Оценка TAE была получена в модели Вестгарда в соответствии с рекомендациями CLSI EP17-A2[10] с критерием, [(абсолютная систематическая ошибка) + 2 CO ≤ 1 $\log_{10}$ МЕ/мл]. Подход с разностью двух измерений оценивался с использованием критерия [(2 x кв. корень (2) x CO) ≤ 1 $\log_{10}$ МЕ/мл].

Результаты определения LLOQ для каждого образца представлены в Таблица 5.

Таблица 5. Определение LLoQ для теста Xpert HBV VL

Генотип ВГВ	Партия	N	Концентрация ВГВ (log_{10} МЕ/мл)		Систематическая ошибка	Общее СО	Общая аналитическая ошибка (Total Analytical Error, TAE)[a]	Подход с двумя измерениями[b]
			Ожидаемая	Наблюдаемая				
A	1	24	1,00	1.02	0,02	0,20	0,42	0,57
	2	24	1,00	1,05	0,05	0,16	0,37	0,45
	3	24	1,00	0,94	-0,06	0,20	0,46	0,57
	4	23	1,00	1.02	0,02	0,14	0,30	0,40
B	1	16	1,00	1,18	0,18	0,11	0,39	0,30
	2	24	1,00	1,18	0,18	0,17	0,53	0,49
	3	8	1,00	1,17	0,17	0,19	0,54	0,53
	4	8	1,00	1,25	0,25	0,19	0,64	0,55
C	1	16	1,00	1,10	0,10	0,17	0,44	0,47
	2	24	1,00	1,11	0,11	0,22	0,55	0,61
	3	8	1,00	0,83	-0,17	0,24	0,65	0,68
	4	8	1,00	1,01	0,01	0,18	0,36	0,50
D	1	16	1,00	0,81	-0,19	0,28	0,74	0,78
	2	24	1,00	0,79	-0,21	0,27	0,75	0,76
	3	8	1,00	0,83	-0,14	0,14	0,42	0,39
	4	8	1,00	0,91	-0,09	0,11	0,31	0,32

[a] Значения общей аналитической ошибки, вычисленные в модели Вестгарда, где: [TAE = |систематическая ошибка | + (2×CO) ≤ 1 log_{10} МЕ/мл], что обеспечивает 95 %-ную вероятность того, что измерение будет отличаться от истинного значения менее чем на 1 log_{10} МЕ/мл.

[b] Подход с двумя измерениями [2 × (SQRT(2) × SD) ≤ 1 log_{10} МЕ/мл] показал, что отличие менее 1 log_{10} МЕ/мл может объясняться случайной ошибкой измерения.

Эти результаты показывают, что тест Xpert HBV VL позволяет определять ДНК ВГВ в концентрации 10 МЕ/мл с приемлемыми правильностью и прецизионностью.

18.3 Прецизионность/воспроизводимость

Прецизионность и воспроизводимость теста Xpert HBV VL определяли с использованием образцов плазмы с K_2ЭДТА при помощи дисперсионного анализа (ANOVA) для определения общей дисперсии.

Было проведено многоцентровое (3 центра; 2 внешних и 1 внутренний) слепое исследование с целью определения основных компонентов дисперсии теста Xpert HBV VL с применением восьмикомпонентной панели, состоящей из восьми ВГВ-положительных образцов. ВГВ-положительные компоненты панели готовили путем разведения ВГВ-плазмид с хорошо изученными характеристиками или ВГВ-положительного клинического образца в человеческой плазме с ЭДТА. По два оператора (один с опытом выполнения ПЦР, другой без такого опыта) в каждом из трех исследовательских центров исследовали одну панель в двух повторах два раза в день (что равноценно восьми повторам в день) на протяжении шести дней. Всего выполнено 144 повторов на каждый компонент панели. Были использованы три партии теста Xpert HBV VL, каждая на протяжении двух дней исследований. Прецизионность и воспроизводимость определяли в соответствии с CLSI EP05-A3[11] и CLSI EP15-A3.[12]

Прецизионность и воспроизводимость теста Xpert HBV VL оценивали методом иерархического дисперсионного анализа, где в качестве факторов использованы следующие: центр/анализатор, партия, день, оператор/серия, в пределах серии. Рассчитывали стандартное отклонение и процент вариабельности концентрации ВГВ, представленной в виде log_{10}, под влиянием каждого фактора, как показано в Таблица 6.

Таблица 6. Прецизионность и воспроизводимость теста Xpert HBV VL

Концентрация ДНК ВГВ (log_{10} МЕ/мл)			Влияние на СО общей вариабельности (КВ%)										Общая прецизионность	
			Центр/прибор		Партия		День		Оператор/ серия		В пределах цикла			
Ожидаемая	Наблюдаемая	N	СО	(%)[a]	СО	(%) [a]	СО	(%) [a]	СО	(%) [a]	СО	(%) [a]	СО	КВ (%)[b]
9,00	9.13[c]	144	<0,01	<0,01	0,04	23,4	<0,01	<0,01	0,02	4,9	0,07	71,7	0,08	19,7
8,00	8,17	144	<0,01	<0,01	0,04	26,7	<0,01	<0,01	0,02	5,4	0,06	67,9	0,07	16,9
7,00	7,15	144	0,01	2,2	0,03	12,2	0,01	3,9	<0,01	<0,01	0,07	81,8	0,07	16,8
6,00	6,18	144	<0,01	<0,01	0,04	32,1	0,01	4,3	<0,01	<0,01	0,05	63,6	0,06	14,7
4,70	4,87	144	0,02	4,5	0,03	15,3	<0,01	<0,01	<0,01	<0,01	0,07	80,2	0,07	17,1
3,00	3,19	144	<0,01	<0,01	0,03	28,8	<0,01	<0,01	0,02	11,5	0,04	59,7	0,06	13,2
2,00	2,17	144	<0,01	<0,01	0,02	8,6	<0,01	<0,01	0,01	1,0	0,08	90,5	0,08	19,0
1,00	1,13	144	<0,01	<0,01	<0,01	<0,01	0,05	11,0	0,01	0,3	0,15	88,8	0,16	37,7

[a] (%) представляет собой влияние компонента дисперсии на общую дисперсию

[b] «КВ» является логнормальным КВ, полученным по формуле: $Lognormal\ CV(\%) = 100 * \sqrt{10^{\left(\ln(10)*\sigma^2_{log10\_data}\right)} - 1}$

[c] Наблюдавшееся значение превышает диапазон количественного определения теста Xpert HBV VL.

18.4 Линейный диапазон

Генотип A

Линейный диапазон теста Xpert HBV VL определяли путем анализа панелей из восьми образцов, включавших диапазон концентраций от 1,00 до 9,00 log_{10} МЕ/мл. Панели готовили путем внесения клинического образца, содержащего ВГВ генотипа A, или архивной ДНК-плазмиды ВГВ в высоком титре, в отрицательную на ВГВ сыворотку и плазму с ЭДТА. Каждый компонент панели исследовали в восьми повторах на партию реагентов, за исключением самых низких разведений, которые исследовали в шестнадцати повторах на партию реагентов. Использовали две партии реагентов. Результаты представлены в Рисунок 9 и Рисунок 10.

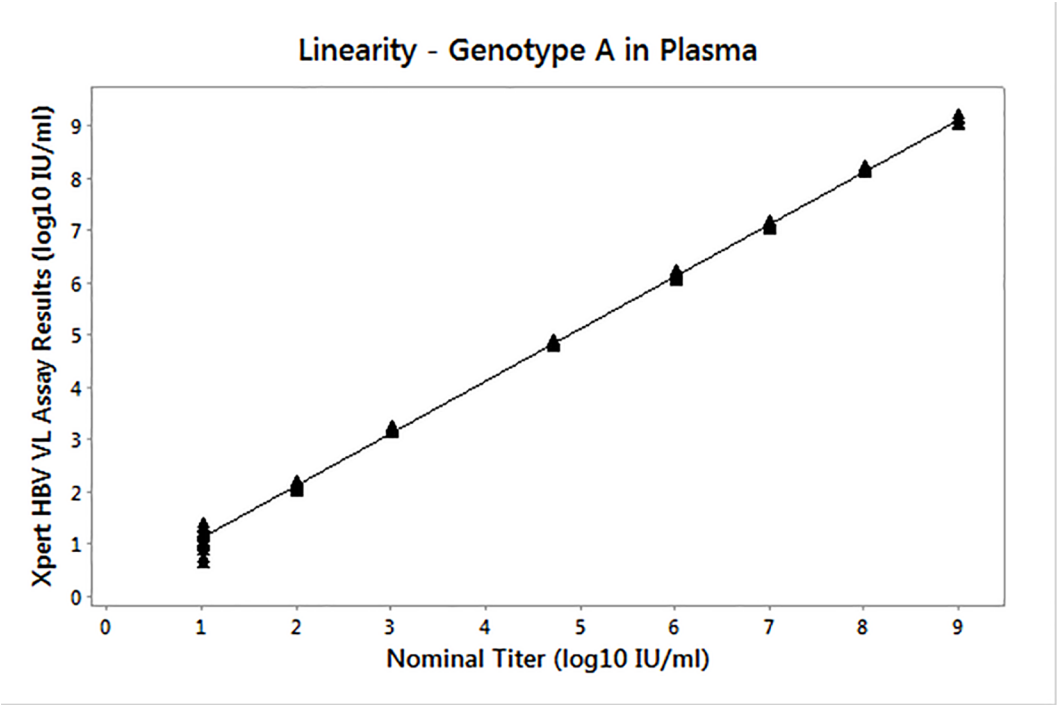

Рисунок 9. Линейность теста Xpert BV VL при исследовании образцов плазмы с ЭДТА

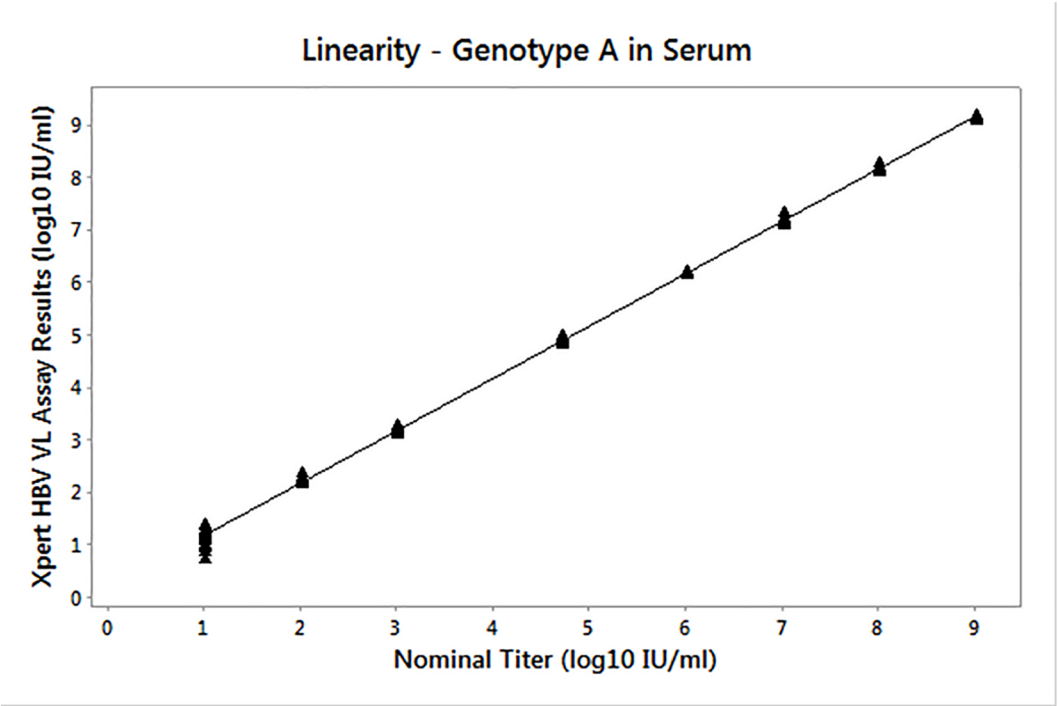

Рисунок 10. Линейность теста Xpert BV VL при исследовании образцов сыворотки с ЭДТА

Генотипы B-H

Для подтверждения линейности были приготовлены панели разведения с генотипами ВГВ от B до H, с целью включить как можно более широкий диапазон измерений. Для этого клинические образцы, соответствующие каждому генотипу ВГВ, разводили в отрицательной на ВГВ плазме с ЭДТА. Компоненты панели тестировали с использованием одной партии реагентов, количество повторов на каждый компонент было таким же, как и для ВГВ генотипа A.

Была продемонстрирована линейность в соответствии с рекомендациями CLSI EP06-A[13] для генотипов A-H со значением R^2 >0,99. Тест Xpert HBV VL дает линейные результаты в диапазоне 1,00–9,00 log_{10} МЕ/мл для генотипа A и во всем исследованном диапазоне для генотипов от B до H (см. Таблица 7).

Таблица 7. Линейность теста Xpert HBV VL по генотипу

Генотип	Уравнение линейной регрессии	R^2	Исследованный диапазон титров (log_{10} МЕ/мл)
A (плазма)	y = 1,005x + 0,093	0,999	1,00–9,00
A (сыворотка)	y = 1,000x + 0,167	0,999	1,00–9,00
B	y = 0,998x – 0,027	0,995	1,00–6,83
C	y = 0,998x – 0,119	0,998	1,00–7,69
D	y = 0,993x + 0,101	0,998	1,00–7,41
E	y = 1,010x – 0,149	0,999	1,00–8,14
F	y = 0,994x – 0,068	0,999	1,00–7,96
G	y = 0,990x + 0,538	0,999	1,00–8,61
B	y = 0,991x + 0,122	0,999	1,00–6,35

18.5 Аналитическая специфичность (эксклюзивность)

Аналитическую специфичность теста Xpert HBV VL оценивали путем внесения микроорганизмов и вирусов, способных давать перекрестные реакции, в концентрации 1×10^6 КОЕ/мл для микроорганизмов и 1×10^5 копий/мл или $ЦПД_{50}$/мл для вирусов в ВГВ-отрицательную плазму с ЭДТА и в плазму с ЭДТА, содержащую около 30 МЕ/мл эталонного материала ВГВ (4-й международный стандарт ВОЗ для ВГВ, код NIBSC: 10/266)[4]. Исследованные микроорганизмы перечислены в Таблица 8. Ни один из исследованных организмов не дал перекрестной реакции и не препятствовал количественному определению в тесте Xpert HBV VL.

Таблица 8. Аналитическая специфичность, микроорганизмы

Вирусы		Бактерии	Дрожжи
Вирус полиомы человека BK	Вирус иммунодефицита человека 1	*Staphylococcus epidermidis*	*Candida albicans*
Цитомегаловирус	Вирус иммунодефицита человека 2	*Staphylococcus aureus*	
Вирус Эпштейна-Барр	Вирус папилломы человека типа 16		
Вирус гепатита A	Вирус папилломы человека типа 18		
Вирус гепатита C	Т-лимфотропный вирус человека, тип 1		
Вирус простого герпеса, тип 1	Т-лимфотропный вирус человека, тип 2		
Вирус простого герпеса, тип 2	Вирус ветряной оспы		
Вирус герпеса человека 6 типа	Вирус осповакцины		
Вирус герпеса человека типа 8			

18.6 Субстанции, вероятно препятствующие проведению анализа

Оценивали подверженность теста Xpert HBV VL влиянию повышенных уровней эндогенных веществ, маркеров аутоиммунных заболеваний и назначаемых ВГВ-инфицированным пациентам лекарств. Ингибирующий эффект изучали в отсутствии и присутствии около 30 МЕ/мл эталонного материала ДНК ВГВ (4-й международный стандарт ВОЗ для ВГВ, код NIBSC: 10/266).[4]

Было установлено, что повышенные уровни эндогенных веществ, перечисленных в Таблица 9, не препятствуют количественной оценке теста Xpert HBV VL со средним титром $\log_{10}$ каждого из положительных образцов ВГВ, содержащих потенциально мешающие вещества в пределах ± 0,10 $\log_{10}$ МЕ/мл от значения положительного контроля. Отрицательные результаты были получены для всех образцов, не содержащих ВГВ, что указывает на отсутствие влияния на специфичность теста.

Эндогенные вещества

Таблица 9. Эндогенные субстанции и применявшиеся в анализе концентрации

Субстанция	Концентрация, применявшаяся в анализе
Альбумин	9 г/дл
Билирубин	20 мг/дл
Гемоглобин	500 мг/дл
ДНК человека	0,4 мг/дл
Триглицериды	3000 мг/дл

Лекарственные препараты

Установлено, что перечисленные в Таблица 10 лекарственные препараты в концентрациях, в 3 раза превышающих максимальную концентрацию в плазме (C_{max}), в присутствии или отсутствии ДНК ВГВ, не оказывают влияния на количественные показатели, получаемые при помощи теста Xpert HBV VL, или на его специфичность.

Таблица 10. Пулы препаратов, применявшиеся в анализе

Пул	Лекарственные препараты
1	Зидовудин, саквинавир кларитромицин, интерферон-альфа-2b, ритонавир, омбитасвир, паритапревир, дасабувир, диданозин
2	Абакавира сульфат, фосампренавир, пегинтерферон-альфа-2a, рибавирин, энтекавир, адефовира дипивоксил
3	Тенофовира дизопроксила фумарат, ламивудин, индинавира сульфат, ганцикловир, валганцикловира гидрохлорид, ацикловир, пароксетин, телбивудин
4	Ставудин, эфавиренз, лопинавир, энфувиртид, ципрофлоксацин, флуоксетин
5	Невирапин, нелфинавир, азитромицин, валацикловир, сертралин, тенофовира алафенамид

Маркеры аутоиммунных заболеваний

При исследовании образцов плазмы с K_2ЭДТА, содержащих маркеры аутоиммунных заболеваний (каждый маркер был взят у пяти положительный пациентов), не было выявлено влияния на функциональные характеристики теста Xpert HBV VL маркеров системной красной волчанки (СКВ), антинуклеарных антител (АНА) или ревматоидного фактора (РФ). Средняя концентрация ДНК ВГВ (представленная в виде $\log_{10}$), которая вносилась в образцы, находилась в пределах ± 0,10 $\log_{10}$ МЕ/мл относительно положительного контроля. Отрицательные результаты были получены для всех образцов, не содержащих ВГВ, что указывает на отсутствие влияния на специфичность теста.

18.7 Эквивалентность материалов (плазма с K_2ЭДТА, PPT-ЭДТА и сыворотка)

Исследование эквивалентности материалов для теста Xpert HBV VL было проведено с использованием 32 соответствующих по характеристикам ВГВ-положительных клинических образцов и 23 соответствующих по характеристикам ВГВ-отрицательных клинических образцов, собранных в пробирки для сбора плазмы с K_2-ЭДТА, пробирки для сбора плазмы PPT-ЭДТА и пробирки для сбора сыворотки. В 23 соответствующих по характеристикам ВГВ-отрицательных клинических образца вносили клинические образцы с ВГВ, соответствующие генотипам от B до G, а также ДНК-плазмиды, экспрессирующие целевую последовательность генома генотипа A, в титрах по всему линейному диапазону.

На исследованных образцах была продемонстрирована эквивалентность материалов (см. Рисунок 11 и Рисунок 12).

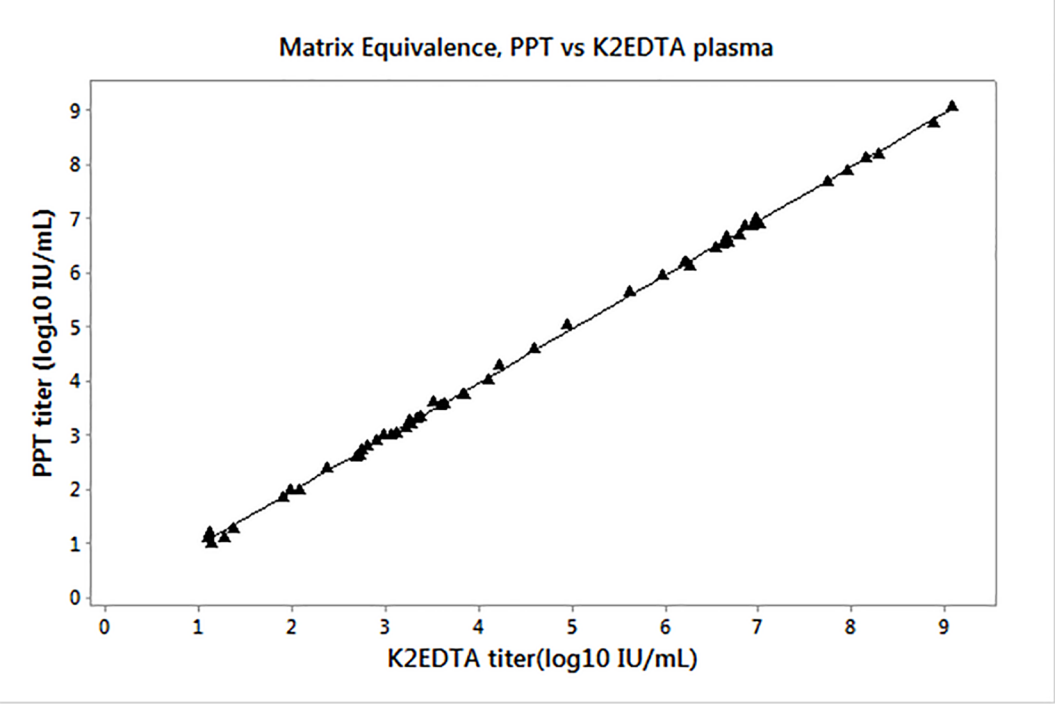

Рисунок 11. График линейной регрессии, плазма в пробирках PPT-ЭДТА по сравнению с плазмой в пробирках с K_2-ЭДТА

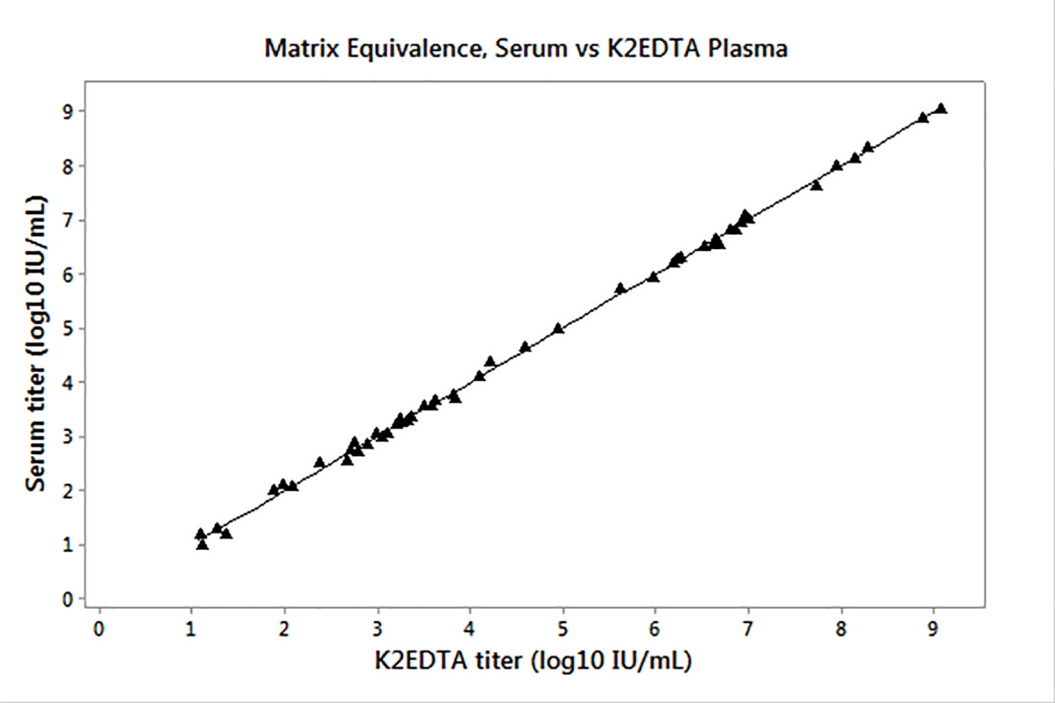

Рисунок 12. График линейной регрессии, сыворотка по сравнению с плазмой в пробирках с K_2-ЭДТА

Результаты показывают, что тест Xpert HBV VL эквивалентно работает в плазме K_2-ЭДТА, плазме PPT-ЭДТА и сыворотке для образцов в диапазоне приблизительно 1,0–9,0 log10 МЕ/мл.

18.8 Отказ всей системы

Частоту отказа всей системы для теста HBV VL определяли путем тестирования в 100 повторах образца плазмы с ЭДТА, в который был внесен ВГВ генотипа A в виде 4-го международного стандарта ВОЗ для ДНК ВГВ (код NIBSC 10/266)[4]. Тестировали образцы с внесенной вирусной ДНК в концентрации около 3 x LLOQ (30 МЕ/мл).

Результаты исследования показали, что все повторы были действительными, с положительным результатом в отношении целевой последовательности ВГВ, а частота отказа всей системы составила 0,0 %

18.9 Контаминация продуктами предыдущей реакции

Выполняли тестирование ВГВ-положительного образца с высоким титром (>1 x 10^7 МЕ/мл) и сразу после этого тестировали ВГВ-отрицательный образец на том же модуле GeneXpert. Процедуру повторяли двадцать (20) раз на двух модулях. Частота контаминации продуктами предыдущей реакции в тесте Xpert HBV VL составила 0 %.

19 Клинические функциональные характеристики

19.1 Специфичность у здоровых доноров крови

Специфичность теста Xpert HBV VL оценивали с использованием 99 образцов сыворотки и 100 образцов плазмы с ЭДТА, полученных от ВГВ-отрицательных доноров крови. Специфичность теста Xpert HBV VL составила 100,0 % [95 % ДИ: 98,1–100,0 (199/199)].

19.2 Корреляция между методами

Было проведено многоцентровое исследование для сравнения функциональных характеристик теста Xpert HBV VL с методом сравнения, предназначенным для количественного определения ДНК ВГВ. Для этого были использованы оставшиеся образцы сыворотки и плазмы с ЭДТА, полученные в рамках оказания стандартной медицинской помощи у лиц, инфицированных ВГВ.

Из 876 пригодных к анализу пациентов 351 (40,1 %) были женского пола и 489 (55,8%) были мужского пола. Средний возраст составил 47,2 ± 15,9 лет, диапазон возраста — от 18 до 89 лет. Из 876 образцов 560 содержали ДНК ВГВ в диапазоне количественного определения обоих тестов — Xpert HBV VL и метода сравнения. Результаты анализа с использованием регрессии Деминга и обычной линейной регрессии представлены в Рисунок 13.

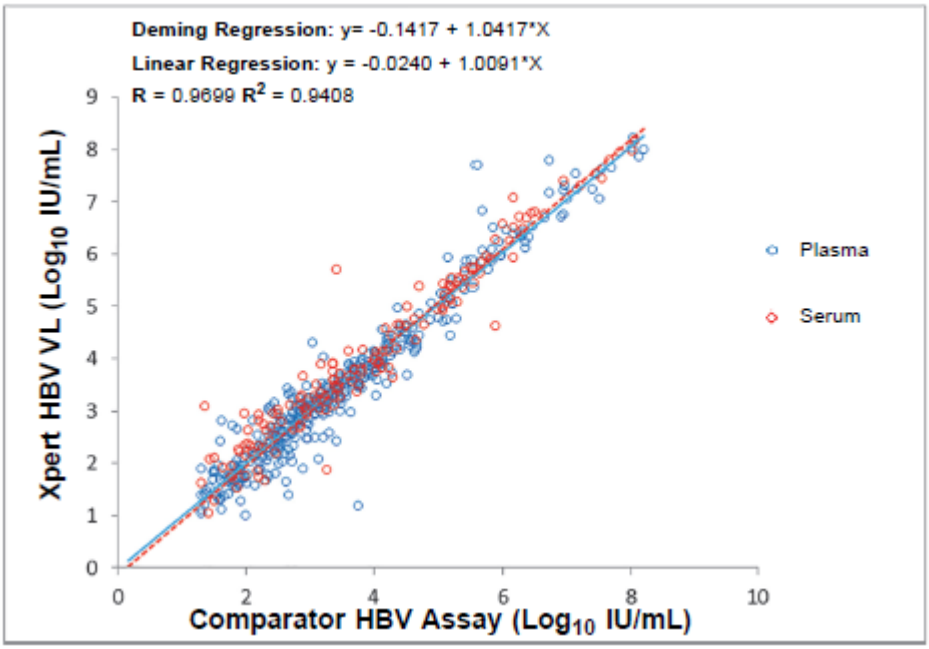

Рисунок 13. Корреляция между результатами теста Xpert HBV VL и метода сравнения при использовании образцов сыворотки и плазмы с ЭДТА

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21 Расположение штаб-квартиры корпорации Cepheid

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22 Техническая поддержка

Прежде чем обращаться в службу технической поддержки компании Cepheid, подготовьте следующую информацию:

- Название изделия
- Номер партии
- Серийный номер прибора
- Сообщения об ошибках (если имеются)
- Версия программного обеспечения и, при наличии, сервисный номер компьютера

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Электронный адрес: techsupport@cepheid.com	Электронный адрес: support@cepheideurope.com

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23 Условные обозначения

Символ	Значение
	Номер по каталогу
	Медицинское изделие для диагностики*in vitro*
	Не использовать повторно
	Код партии
	См. инструкцию по применению
	Производитель
	Страна производства
	Содержит достаточное количество для *n* тестов
	Контроль
	Срок годности
	Маркировка CE – Европейское соответствие
	Температурные ограничения
	Биологические риски
	Предупреждение
	Предупреждение
	Уполномоченный представитель в Швейцарии
	Импортер

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2 Common or Usual Name

HCV VL

3 Intended Use

The HCV VL assay, performed on GeneXpert® Instrument Systems, is designed for the rapid quantitation of Hepatitis C Virus (HCV) RNA in human serum or plasma (EDTA) from HCV-infected individuals. The test utilizes automated reverse transcriptase polymerase chain reaction (RT-PCR) using fluorescence to detect the RNA of interest for the quantitation of HCV.

The HCV VL assay quantifies HCV genotypes 1–6 over the range of 10 to 100,000,000 IU/mL. The HCV VL assay is intended for use as an aid in the management of HCV infected patients undergoing antiviral therapy. The test measures HCV RNA levels at baseline and during treatment and can be utilized to predict sustained and nonsustained virological responses to HCV therapy.

Results from the HCV VL assay may also be used to confirm HCV infection in anti-HCV positive individuals. In anti-HCV positive individuals who test negative for HCV RNA, use of another HCV antibody assay may be considered for distinction between true HCV exposure and biologic false positivity. Repeat HCV RNA testing may be indicated in cases that have had HCV exposure in the last 6 months or have clinical evidence of HCV disease.

The Xpert HCV VL assay is intended to be used by laboratory professionals or specifically-trained healthcare workers.

The assay is not intended to be used as a donor screening test for HCV.

4 Summary and Explanation

HCV is a member of the Flaviviridae family and has been recognized as the major causative agent of chronic liver disease, including chronic active hepatitis, cirrhosis and hepatocellular carcinoma.[1] The HCV genome is a positive-sense RNA molecule of approximately 9500 nucleotides.[1] HCV is usually transmitted through percutaneous exposure to infected blood, primarily by intravenous drug use and receipt of unscreened donated blood products. Less frequently, HCV has been shown to be transmitted through occupational, perinatal and sexual exposures.[2]

An estimated 185 million people, or roughly 3% of the world's population, have been infected with HCV, and over 80% live in Low and Middle Income Countries (LMICs).[3] The burden of disease is greatest in developing countries; the highest reported prevalence is in China (3.2%)[4] Pakistan (4.8%)[4], Nigeria (18.3%)[5] and Egypt (22%).[4] About 15 million European adults are infected with HCV and most of these people are unaware of their infection.[6] Each year, 350,000 to 500,000 people die from HCV-related liver disease.[7]

Antiviral medicines can cure HCV, but access to diagnosis and treatment is low.[7] A cure for HCV infection is now possible in most patients with highly effective, safe and tolerable combinations of oral direct-acting antivirals (DAAs) taken for 8–24 weeks.[5] Eradication of HCV is being discussed for the first time.[5]

Quantitation of HCV RNA has proven useful in providing a metric to evaluate the effectiveness of antiviral response to HCV treatment. Guidelines for the management and treatment of HCV recommend quantitative testing for HCV RNA before the start of antiviral therapy, during therapy, and after the conclusion of treatment. The primary objective of treatment is Sustained Virologic Response (SVR), defined as undetectable HCV RNA by a sensitive test 12 or 24 weeks after the end of treatment depending on the anti-HCV therapy.[8]

5 Principle of the Procedure

The GeneXpert Instrument Systems automate and integrate sample purification, nucleic acid amplification, and detection of the target sequence in simple or complex samples using RT-PCR which uses fluorescence to detect the RNA of interest. The systems consist of an instrument, personal computer, and preloaded software for running tests and viewing the results. The systems require the use of single-use disposable GeneXpert cartridges that hold the RT-PCR reagents and host the RT-PCR processes. Because the cartridges are self-contained, cross-contamination between samples is minimized. For a full description of the systems, refer to the appropriate *GeneXpert Dx Operator Manual* or *GeneXpert Infinity Operator Manual*.

The HCV VL assay includes reagents for the detection of HCV RNA in specimens as well as two internal controls used for quantitation of HCV RNA. The internal controls monitor recovery and the presence of inhibitor(s) in the RT and PCR reactions. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

6 Reagents

6.1 Materials Provided

The HCV VL assay kit contains sufficient reagents to process 10 specimens or quality control samples. The kit contains the following:

HCV VL Assay Cartridges with Integrated Reaction Tubes	**10**
• Bead 1, Bead 2, and Bead 3 (freeze-dried)	1 of each per cartridge
• Lysis Reagent (Guanidinium Thiocyanate)	2.0 mL per cartridge
• Rinse Reagent	0.5 mL per cartridge
• Elution Reagent	1.5 mL per cartridge
• Binding Reagent	2.4 mL per cartridge
• Proteinase K Reagent	0.48 mL per cartridge
Disposable 1 mL Transfer Pipettes	**10 per kit**
CD	**1 per kit**
• Assay Definition File (ADF)	
• Instructions to import ADF into GeneXpert software	
• Instructions for Use (Package Insert)	

Note Safety Data Sheets (SDS) are available at www.cepheidinternational.com under the **SUPPORT** tab.

Note The bovine serum albumin (BSA) in the beads within this product was produced and manufactured exclusively from bovine plasma sourced in the United States. No ruminant protein or other animal protein was fed to the animals; the animals passed ante- and post-mortem testing. During processing, there was no mixing of the material with other animal materials.

7 Storage and Handling

- Store the HCV VL assay cartridges and reagents at 2–28 °C.
- Do not open the cartridge until you are ready to perform the assay.
- Do not use a cartridge that has leaked.
- Do not use HCV VL assay cartridges and reagents that were previously frozen.
- Do not use reagents or cartridges that have passed the expiration date.

8 Materials Required but Not Provided

- GeneXpert Dx System or GeneXpert Infinity Systems (catalog number varies by configuration): GeneXpert Instrument, computer with proprietary GeneXpert Dx Software Version 4.7b or higher (GeneXpert Dx systems); or Xpertise 6.4b or higher (Infinity-80/Infinity-48s), barcode scanner, and operator manual.
- Printer: If a printer is needed, contact Cepheid Technical Support to arrange for the purchase of a recommended printer.
- Bleach or sodium hypochlorite

9 Warnings and Precautions

- Treat all biological specimens, including used cartridges, as if capable of transmitting infectious agents. Because it is often impossible to know which might be infectious, all biological specimens should be treated with standard precautions. Guidelines for specimen handling are available from the U.S. Centers for Disease Control and Prevention[9] and the Clinical and Laboratory Standards Institute.[10]
- Good laboratory practices and changing gloves between handling specimens are recommended to avoid contamination of specimens or reagents.
- Follow your institution's safety procedures for working with chemicals and handling biological samples.
- Do not substitute HCV VL assay reagents with other reagents.
- Do not open the HCV VL assay cartridge lid except when adding sample.
- Do not use a cartridge that has been dropped after removing it from the packaging.
- Do not shake the cartridge. Shaking or dropping the cartridge after opening the lid may yield invalid results.
- Do not use a cartridge that has a damaged reaction tube.
- Do not use a cartridge that has leaked.
- Each single-use HCV VL assay cartridge is used to process one test. Do not reuse cartridges.
- The single-use disposable pipette is used to transfer one specimen. Do not reuse spent disposable pipettes.
- Wear clean lab coats and gloves. Change gloves between processing each sample.
- In the event of contamination of the work area or equipment with samples or controls, thoroughly clean the contaminated area with a solution of 1:10 dilution of household chlorine bleach or sodium hypochlorite and then 70% ethanol or 70% denatured ethanol. Wipe work surfaces dry completely before proceeding.
- Consult your institution's environmental waste personnel on proper disposal of used cartridges and unused reagents. Check state, territorial, or local regulations as they may differ from national disposal regulations. The material may exhibit characteristics of hazardous waste requiring specific disposal requirements. Institutions should check their hazardous waste disposal requirements.
- Biological specimens, transfer devices, and used cartridges should be considered capable of transmitting infectious agents requiring standard precautions. Follow your institution's environmental waste procedures for proper disposal of used cartridges and unused reagents. These materials may exhibit characteristics of chemical hazardous waste requiring specific disposal. If country or regional regulations do not provide clear direction on proper disposal, biological specimens and used cartridges should be disposed per WHO [World Health Organization] medical waste handling and disposal guidelines.

10 Chemical Hazards[11,12]

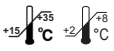
- Signal Word: WARNING
- **UN GHS Hazard Statements:**
  - Harmful if swallowed
  - Causes mild skin irritation
  - Causes eye irritation
- **UN GHS Precautionary Statements:**
  - **Prevention:**
    - Wash thoroughly after handling.
  - **Response:**
    - Call a POISON CENTER of doctor/physician if you feel unwell.
    - If skin irritation occurs: Get medical advice/attention.
    - IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses if present and easy to do. Continue rinsing.
    - If eye irritation persists: Get medical advice/attention.

11 Specimen Collection, Storage, and Transport

Whole blood should be collected in K2-EDTA tubes, EDTA-PPT or serum collection tubes and centrifuged to separate the plasma/serum and red blood cells per the manufacturer's instructions.

- A minimum of 1 mL plasma or serum is required for the HCV VL assay. If using the transfer pipette included in the kit, a minimum of 1.2 mL plasma or serum is required. Alternatively, if using a precision pipette, a minimum of 1 mL plasma or serum is required.

- Whole blood may be held at 15–30 °C for up to 24 hours or at 2–8 °C for up to 3 days prior to plasma/serum preparation. Centrifugation should be performed according to the manufacturer instructions.



- After centrifugation and separation, plasma and serum may be held at 15–35 °C for up to 24 hours or at 2–8 °C for up to 3 days prior to testing.

- Plasma and serum specimens are stable frozen (-70 to -18 °C) for 6 weeks.
- Plasma and serum specimens are stable for up to three freeze/thaw cycles.
- Plasma and serum specimens must be thawed and equilibrated to room temperature prior to transfer to the cartridge.

- Ship whole blood, plasma or serum specimens at 2–8 °C.
- Transportation of whole blood, plasma or serum specimens must comply with country, federal, state and local regulations for the transportation of etiologic agents.

12 Procedure

12.1 Preparing the Specimen

1. Following centrifugation of whole blood samples, 1 mL of plasma can be pipetted directly into the cartridge. Sufficient volume is critical to obtaining valid test results (see instructions in Section 12.2, Preparing the Cartridge Option 1 below).

2. If using frozen specimens, place the specimens at room temperature (20–35 °C) until completely thawed and equilibrated to room temperature before use.

3. Plasma and serum samples stored at 2–8 °C should be removed from the refrigerator and equilibrated to room temperature before use.

4. Plasma samples stored at 2–8 °C or frozen and thawed should be vortexed for 15 seconds before use, if the specimen is cloudy, clarify by a quick centrifugation.

12.2 Preparing the Cartridge

1. Wear protective disposable gloves.
2. Inspect the test cartridge for damage. If damaged, do not use it.
3. Open the lid of the test cartridge.

- **Option 1**: If using the transfer pipette included in the kit (Figure 1), fill to just below the bulb but above the line to transfer at least 1 mL plasma or serum from the collection tube into the sample chamber of the test cartridge (Figure 2). Do **NOT** pour the specimen into the chamber!
- **Option 2**: If using an automatic pipette, transfer at least 1 mL of plasma or serum into the sample chamber of the test cartridge (Figure 2). Do **NOT** pour the specimen into the chamber!

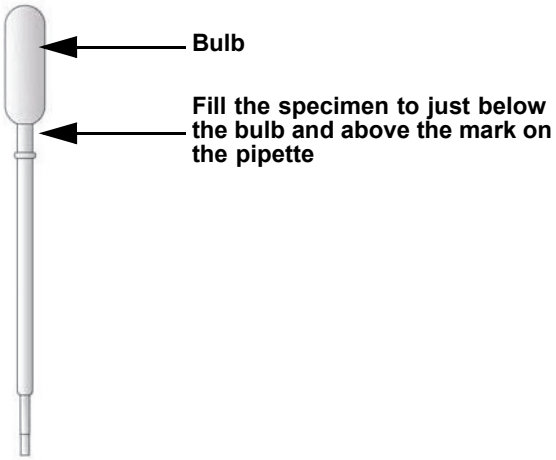


Figure 1. HCV VL Assay Transfer Pipette

4. Close the cartridge lid.
5. Load the cartridge into the GeneXpert Dx instrument or Infinity system.

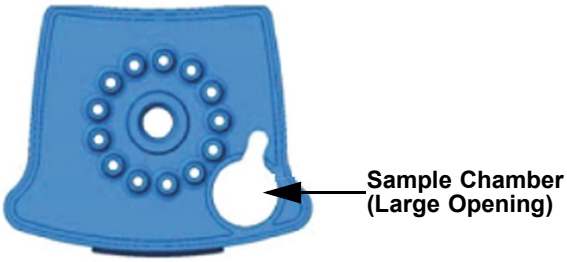


Figure 2. HCV VL Assay Cartridge (Top View)

12.3 Starting the Test

Important **Before you start the test, make sure the HCV VL Assay Definition File (ADF) is imported into the software.**

Note The steps you follow can be different if the system administrator changed the default workflow of the system.

This section lists the basic steps for running the test. For detailed instructions, see the *GeneXpert Dx System Operator Manual* or the *GeneXpert Infinity System Operator Manual*, depending on the model that is being used.

1. Turn on the GeneXpert instrument:
   - If using the GeneXpert Dx instrument, first turn on the instrument and then turn on the computer. The GeneXpert software will launch automatically. If it doesn't, double-click the GeneXpert Dx software shortcut icon on the Windows® desktop.

     or

   - If using the GeneXpert Infinity instrument, power up the instrument. The GeneXpert software will launch automatically. If it doesn't, double-click the Xpertise software shortcut icon on the Windows® desktop.
2. Log on to the GeneXpert Instrument System software using your user name and password.
3. In the GeneXpert System window, click **Create Test** (GeneXpert Dx) or **Orders** and **Order Test** (Infinity).
4. Scan in the Patient ID (optional). If typing the Patient ID, make sure the Patient ID is typed correctly. The Patient ID is associated with the test results and is shown in the View Results window.
5. Scan or type in the Sample ID. If typing the Sample ID, make sure the Sample ID is typed correctly. The Sample ID is associated with the test results and is shown in the View Results window and all reports. The Scan Cartridge dialog box appears.
6. Scan the barcode on the HCV VL assay cartridge. The Create Test window appears. Using the barcode information, the software automatically fills the boxes for the following fields: Select Assay, Reagent Lot ID, Cartridge SN, and Expiration Date.
7. Click **Start Test** (GeneXpert Dx) or **Submit** (Infinity). Enter your password, if requested.
8. For the GeneXpert Infinity System, place the cartridge on the conveyor belt. The cartridge will be automatically loaded, the test will run, and the used cartridge will be placed into the waste container.

   or

   For the GeneXpert Dx Instrument:

   A. Open the instrument module door with the blinking green light and load the cartridge.

   B. Close the door. The test starts and the green light stops blinking. When the test is finished, the light turns off.

   C. Wait until the system releases the door lock before opening the module door and removing the cartridge.

   D. The used cartridges should be disposed in the appropriate specimen waste containers according to your institution’s standard practices.

13 Viewing and Printing Results

This section lists the basic steps for viewing and printing results. For more detailed instructions on how to view and print the results, see the *GeneXpert Dx System Operator Manual* or the *GeneXpert Infinity System Operator Manual*, depending on the instrument used.

1. Click the **View Results** icon to view results.
2. Upon completion of the test, click the **Report** button of the View Results window to view and/or generate a PDF report file.

14 Quality Control

CONTROL

Each test includes a Sample Volume Adequacy (SVA), Internal Quantitative Standard High and Low (IQS-H and IQS-L, also acts a specimen processing control [SPC]) and Probe Check Control (PCC).

- **Sample Volume Adequacy (SVA) –** Ensures the sample was correctly added to the cartridge. The SVA verifies that the correct volume of sample has been added in the sample chamber. The SVA passes if it meets the validated acceptance criteria. If the SVA does not pass, an **ERROR 2096** will be displayed if there is no sample or an **ERROR 2097** will be displayed if there is not enough sample. The system will prevent the user from resuming the test.
- **Internal Quantitative Standard High and Low (IQS-H and IQS-L) –** IQS-H and IQS-L are two Armored RNA® constructs in the form of a dry bead that goes through the whole assay process. The IQS-H and IQS-L are standards calibrated against the WHO 4th International standard for HCV. They are used for quantification by using lot specific parameters for the calculation of HCV RNA concentration in the sample. Additionally IQS-H and IQS-L detect specimen-associated inhibition of the RT-PCR reaction. The IQS-H and IQS-L pass if they meet the validated acceptance criteria.
- **Probe Check Control (PCC)** – Before the start of the PCR reaction, the GeneXpert Instrument System measures the fluorescence signal from the probes to monitor bead rehydration, reaction tube filling, probe integrity and dye stability. The PCC passes if it meets the validated acceptance criteria.
- **External Controls –** Following good laboratory practices, external controls, not available in the kit, should be used in accordance with local, state, and federal accrediting organizations' requirements as applicable.

15 Interpretation of Results

The results are interpreted automatically by the GeneXpert Instrument System from measured fluorescent signals and embedded calculation algorithms and are clearly shown in the View Results window (Figure 3 and Figure 5). Possible results are shown in Table 1.

Table 1. HCV VL Assay Results and Interpretation

Result	Interpretation
HCV DETECTED **XX IU/mL (log X.XX)** See Figure 3.	The HCV RNA is detected at XX IU/mL. • The HCV RNA has a titer within the linear range setting of the assay and the endpoint above the minimum. • IQS-H and IQS-L: PASS. • Probe Check: PASS; all probe check results pass.
HCV DETECTED **> 1.00E08 IU/mL** See Figure 4.	The HCV RNA is detected above the quantitative range of the assay. • IQS-H and IQS-L: PASS. • Probe Check: PASS; all probe check results pass.
HCV DETECTED **< 10 IU/mL** See Figure 5.	The HCV RNA is detected below the quantitative range of the assay. • IQS-H and IQS-L: PASS. • Probe Check: PASS; all probe check results pass.
HCV NOT DETECTED See Figure 6.	The HCV RNA is not detected. • HCV RNA is not detected. • IQS-H and IQS-L: PASS. • Probe Check: PASS; all probe check results pass.
INVALID See Figure 7.	Presence or absence of the HCV RNA cannot be determined. Repeat test according to the instructions in Section 16.2, Retest Procedure. • IQS-H and/or IQS-L: FAIL; Cycle thresholds (Cts) are not within valid range and the endpoint is below the minimum setting. • Probe Check: PASS; all probe check results pass.

Table 1. HCV VL Assay Results and Interpretation (Continued)

Result	Interpretation
ERROR See Figure 8.	Presence or absence of HCV RNA cannot be determined. Repeat test according to the instructions in Section 16.2, Retest Procedure. • Probe Check: FAIL*; all or one of the probe check results fail. * If the probe check passed, the error is caused by the maximum pressure limit exceeding the acceptable range or by a system component failure.
NO RESULT	Presence or absence of HCV RNA cannot be determined. Repeat test according to the instructions in Section 16.2, Retest Procedure. A **NO RESULT** indicates that insufficient data were collected. For example, the operator stopped a test that was in progress.

Note Assay screenshots are for example only. Assay name and version number may vary from the screenshots shown in this package insert.

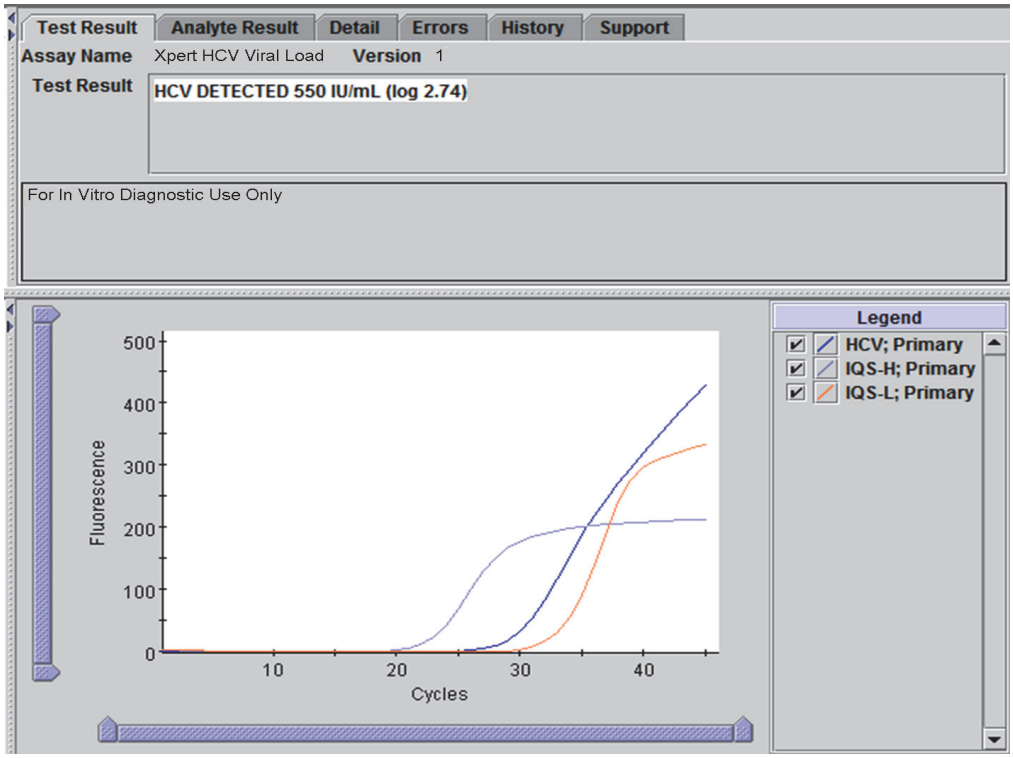


Figure 3. HCV Detected and Quantified

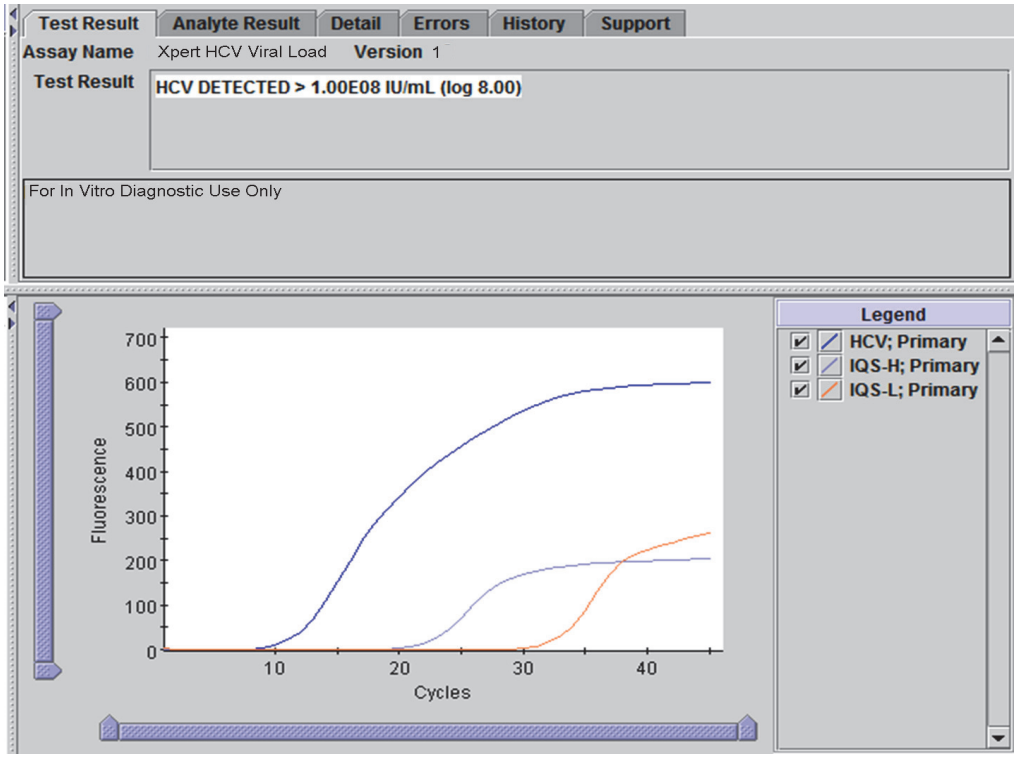


Figure 4. HCV Detected

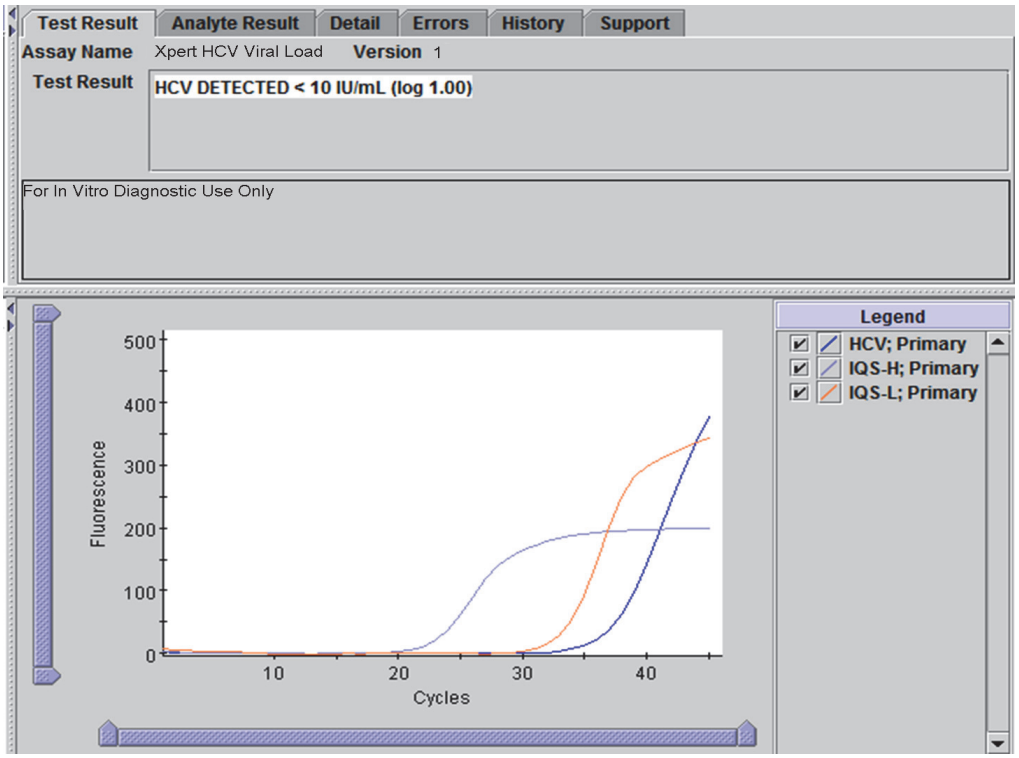


Figure 5. HCV Detected

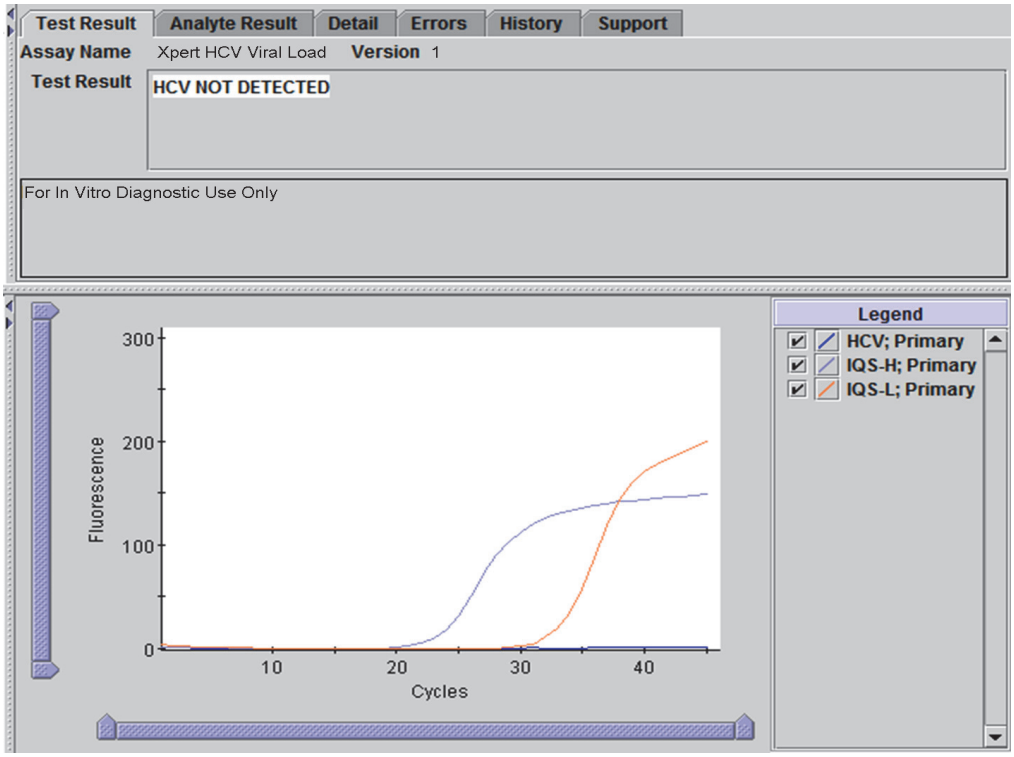


Figure 6. HCV Not Detected

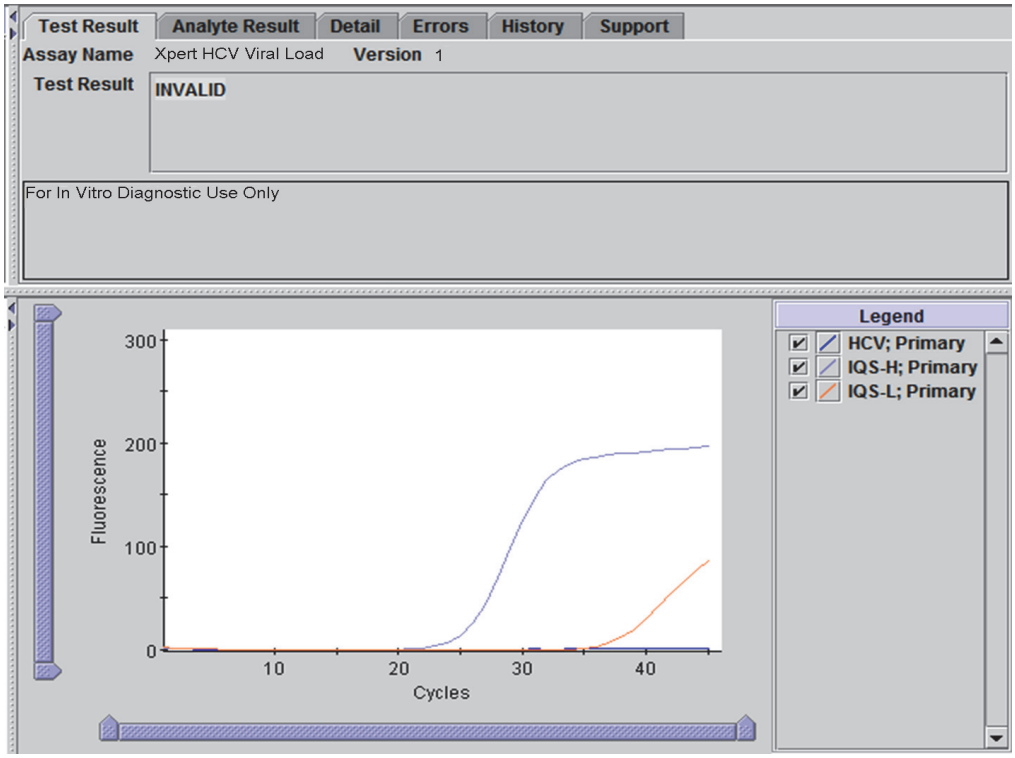


Figure 7. Invalid

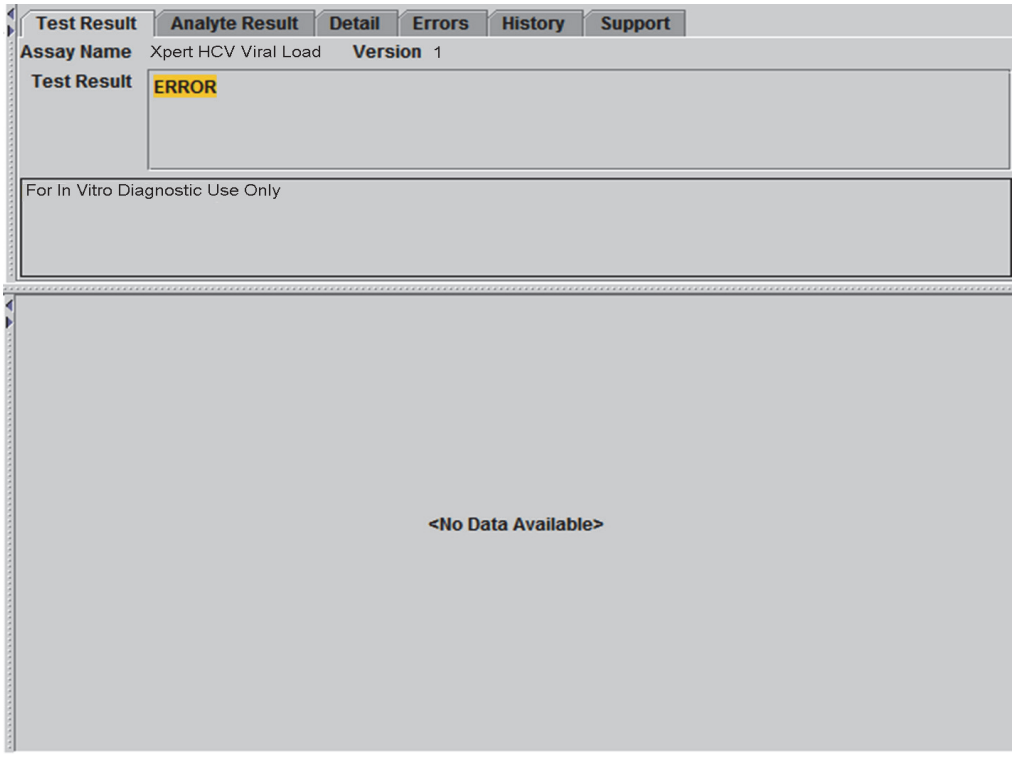


Figure 8. Error

16 Retests

16.1 Reasons to Repeat the Assay

If any of the test results mentioned below occur, repeat the test according to the instructions in Section 16.2, Retest Procedure.

- An **INVALID** result indicates one or more of the following:
  - The IQS-H and/or IQS-L Cts are not within valid range.
  - The sample was not properly processed or PCR was inhibited.
- An **ERROR** result indicates that the assay was aborted. Possible causes include: insufficient volume of sample was added, the reaction tube was filled improperly, a reagent probe integrity problem was detected, or the maximum pressure limit was exceeded.
- A **NO RESULT** indicates that insufficient data were collected. For example, the operator stopped a test that was in progress, or a power failure occurred.

16.2 Retest Procedure

For retest of a **NO RESULT**, **INVALID**, or **ERROR** result, use a new cartridge (do not re-use the cartridge) and new reagents.

1. Remove a new cartridge from the kit.
2. See Section 12, Procedure, including Section 12.1, Preparing the Specimen, Section 12.2, Preparing the Cartridge, and Section 12.3, Starting the Test.

17 Limitations

Good laboratory practices and changing gloves between handling specimens are recommended to avoid contamination of reagents.

Mutations or polymorphisms in primer or probe binding regions may affect detection of new or unknown HCV variants resulting in a false negative result.

18 Performance Characteristics

18.1 Limit of Detection

The limit of detection (LOD) of the HCV VL assay was determined by testing eight different dilutions prepared from a HCV genotype 1 reference standard in HCV negative EDTA plasma and serum. The HCV genotype 1 material used in the LOD study was the WHO 4th International standard, NIBSC code 06/102. The limit of detection was determined for three reagent lots and a total of 72 or 73 replicates per concentration level were tested. One additional low concentration level was included for both sample types after the first day of testing. The number of tested replicates for this level was thus smaller (49 in plasma and 53 in serum). The evaluation was performed according to CLSI guideline E17-A2. The HCV RNA concentration that can be detected with a positivity rate of greater than 95% was determined by Probit regression analysis and the results for the individual lots and specimens are shown in Table 2. The maximum observed LOD with Probit analysis for HCV genotype 1 in EDTA plasma is 4.0 IU/mL (95% CI 2.8 – 5.2). The maximum observed LOD with Probit analysis for HCV genotype 1 in serum is 6.1 IU/mL (95% CI 4.2 – 7.9).

Table 2. HCV VL LOD Estimates with Probit Regression and 95% Upper and Lower Confidence Intervals for HCV Genotype 1 Specimens in Plasma and Serum per Kit Lot

Specimen	Lot	LOD 95% (IU/mL)	95% CI (IU/mL)
WHO (Plasma)	1	3.3	2.4 - 4.2
	2	4.0	2.7 - 5.2
	3	4.0	2.8 - 5.2
WHO (Serum)	1	6.1	4.2 - 7.9
	2	2.6	1.9 - 3.3
	3	2.3	1.8 - 2.9

Hit rate analysis shows a positivity of > 95% at 6 IU/mL for the HCV genotype 1 material tested as shown in Table 3.

Table 3. HCV VL LOD for HCV Genotype 1 in EDTA Plasma and Serum

Specimen	Concentration (IU/mL)	No. Replicates	No. Positives	Positivity Rate (%)
WHO (Plasma)	0.5[a]	49	24	49
	1	72	47	65
	2	72	61	85
	3	72	69	96
	4	72	67	93
	6	72	71	99
	8	73	73	100
	10	72	72	100
WHO (Serum)	0.5[a]	53	21	40
	1	73	47	64
	2	73	64	88
	3	72	69	96
	4	73	71	97
	6	72	71	99
	8	72	70	97
	10	72	72	100

a. 0.5 IU/mL was added day 2 due to the high positivity rate observed at 1 IU/mL after day 1

In addition, dilutions of clinical specimens representing HCV genotype 1a, 2b, 3a, 4a, 5a and 6a in negative human EDTA plasma were analyzed with one reagent lot and 24 replicates per concentration level. The assignment of the nominal concentration of clinical specimens was determined by Abbott RealTime HCV™ assay. Hit rate analysis shows a positivity of >95% for all genotypes at 10 IU/mL as shown in Table 4.

Table 4. HCV VL LOD Hit Rate Analysis for HCV Genotype 1 – 6 Specimens in EDTA Plasma

Genotype	Lowest Concentration Level > 95% Hit Rate (IU/mL)	Hit Rate (%)
1a	10	100
2b	4	100
3a	6	100
4a	4	100
5a	2	96
6a	4	96

18.2 Limit of Quantitation

The total analytical error (TAE) was calculated using estimates determined through analysis of data from LOD study (WHO standard) and the Precision/Reproducibility study according to CLSI guideline E17-A2. The TAE for the dilutions that had an observed concentration at or near the assay limit of detection 10 IU/mL (1.0 $\log_{10}$) are presented in Table 5. TAE was estimated by two different methods.

Table 5. HCV VL TAE Analysis for Determination of LOQ

Specimen (Study)	DL Lot	N	Concentration (Log10 IU/mL)		Bias	Total SD	TAE[a] Absolute Bias + 2xSD	TAE[b] 2xSQRT (2)xSD
			Expected	Observed				
Acrometrix (Precision)	DL1	72	1.40	1.31	0.09	0.15	0.38	0.41
	DL2	72	1.40	1.29	0.11	0.14	0.40	0.41
	DL3	72	1.40	1.24	0.16	0.12	0.41	0.35
Acrometrix (Precision)	DL1	72	1.00	0.92	0.08	0.22	0.52	0.62
	DL2	72	1.00	0.82	0.18	0.18	0.54	0.51
	DL3	72	1.00	0.75	0.25	0.19	0.63	0.54
WHO, Plasma (LOD)	DL1	24	1.00	0.91	0.09	0.21	0.51	0.59
	DL2	24	1.00	0.82	0.18	0.30	0.78	0.86
	DL3	24	1.00	0.86	0.14	0.17	0.48	0.48
WHO, Serum (LOD)	DL1	24	1.00	0.96	0.04	0.13	0.30	0.37
	DL2	24	1.00	0.88	0.12	0.23	0.58	0.66
	DL3	24	1.00	0.80	0.20	0.18	0.57	0.52

a. TAE calculated according to the Westgard model in CLSI EP17-A2 (Section 6.2)
b. TAE based upon the difference between two measurements approach

The results of the TAE analysis demonstrate that the HCV VL assay can determine 10 IU/mL (1.0 $\log_{10}$) with an acceptable trueness and precision.

18.3 Precision/Reproducibility

The precision/reproducibility of the HCV VL assay was determined by analysis of parallel dilutions of HCV reference materials in HCV negative EDTA plasma. The nominal concentration of the reference material used was calibrated to the WHO 4th HCV International Standard (06/102). The study was a two site, blinded, comparative study using a seven-member panel of HCV reference material in HCV negative EDTA plasma with RNA concentrations that span the HCV VL assay quantitation range. Two operators at each of the two study sites tested one panel of twenty-one samples once per day over six testing days per lot. One site used an Infinity-80 instrument and the other site used GeneXpert Dx instruments. Three lots of HCV VL assay reagents were used for the study. Precision/reproducibility was evaluated in accordance with "Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline" CLSI document EP5-A2. The precision results for each regent lot are shown in Table 6.

Table 6. HCV VL Precision per Lot

Expected HCV RNA Concentration log_{10} IU/mL	Total Precision per Lot					
	Lot 1		Lot 2		Lot 3	
	SD	CV[a]	SD	CV[a]	SD	CV[a]
1.0	0.23	55.8%	0.18	44.2%	0.20	48.1%
1.4	0.15	35.1%	0.15	35.8%	0.13	29.6%
2.7	0.09	20.7%	0.09	20.6%	0.09	20.2%
4.2	0.07	16.4%	0.08	18.9%	0.07	15.3%
5.4	0.12	28.3%	0.09	19.9%	0.07	16.2%
6.9	0.13	31.8%	0.09	20.9%	0.07	17.0%
8.2	0.10	22.7%	0.10	23.7%	0.08	17.8%

a. "CV" is lognormal CV, as obtained using the formula:

$$CV(\text{of the lognormal dist}) = \sqrt{10^{\ln(10)*\sigma^2} - 1}$$

The reproducibility and precision of the HCV VL assay was evaluated by using nested ANOVA with terms for Site/Instrument, Lot, Day, Operator/Run and Within-Run. The standard deviation and the percentage of variability due to each component of the log_{10} HCV transformed concentrations were calculated, see Table 7.

Table 7. Standard Deviation and Contributable Percentage of Variability for Each Term and Total Precision

HCV RNA Concentration log_{10} IU/mL			Contribution to Total Variance SD (CV%)										Total Precision			
			Site/Inst		Lot		Day		Operator/ Run		Within-Run		Total			
Expected	Actual	N	SD	(%)[a]	SD	(%)[a]	SD	(%)[a]	SD	(%)[a]	SD	(%)[a]	SD	Lower CI	Upper CI	CV[b]
1.0	0.83	216	0.03	1.8%	0.08	13.2%	0.04	3.5%	0.00	0.0%	0.19	81.6%	0.21	0.18	0.25	51.7%
1.4	1.28	216	0.00	0.0%	0.04	7.1%	0.00	0.0%	0.00	0.0%	0.14	92.9%	0.14	0.13	0.16	34.1%
2.7	2.66	216	0.00	0.0%	0.04	17.2%	0.00	0.0%	0.02	3.2%	0.08	79.5%	0.09	0.08	0.11	22.1%
4.2	4.18	215	0.00	0.0%	0.05	30.9%	0.01	2.6%	0.00	0.0%	0.07	66.5%	0.09	0.07	0.12	20.6%
5.4	5.44	216	0.00	0.0%	0.06	26.5%	0.00	0.0%	0.01	1.3%	0.09	72.2%	0.11	0.09	0.14	25.8%
6.9	6.86	216	0.00	0.0%	0.07	34.0%	0.02	3.4%	0.00	0.0%	0.10	62.5%	0.13	0.10	0.17	29.8%
8.2	8.11	216	0.00	0.0%	0.09	47.9%	0.00	0.0%	0.02	2.6%	0.09	49.5%	0.13	0.10	0.19	30.5%

a. (%) is contribution of variance component to overall lognormal CV
b. "CV" is lognormal CV, as obtained using the formula:

$$CV(\text{of the lognormal dist}) = \sqrt{10^{\ln(10)*\sigma^2} - 1}$$

18.4 Linear Range and Inclusivity

The linear range of the HCV VL assay was determined by analysis of a twelve member panel covering a range from ~5 (0.75 $\log_{10}$) to ~1 x 10^8 (8 $\log_{10}$) IU/mL. Panels were prepared by parallel dilutions of HCV reference material (Armored RNA® genotype 1 and clinical specimen genotype 1) in HCV negative EDTA plasma and serum. The nominal concentration of the reference material used was calibrated to the WHO 4th HCV International Standard (06/102). Each panel member was tested in replicates of four on each of three testing days using two kit lots. Totally, 24 replicates per panel member and sample type were tested. The linearity analysis was performed according to CLSI guideline EP06-A. The combined results for both lots are shown in Figure 9 and Figure 10. The HCV VL assay is linear within a range 0.8–8.0 $\log_{10}$ IU/mL with a R^2 value of >0.997.

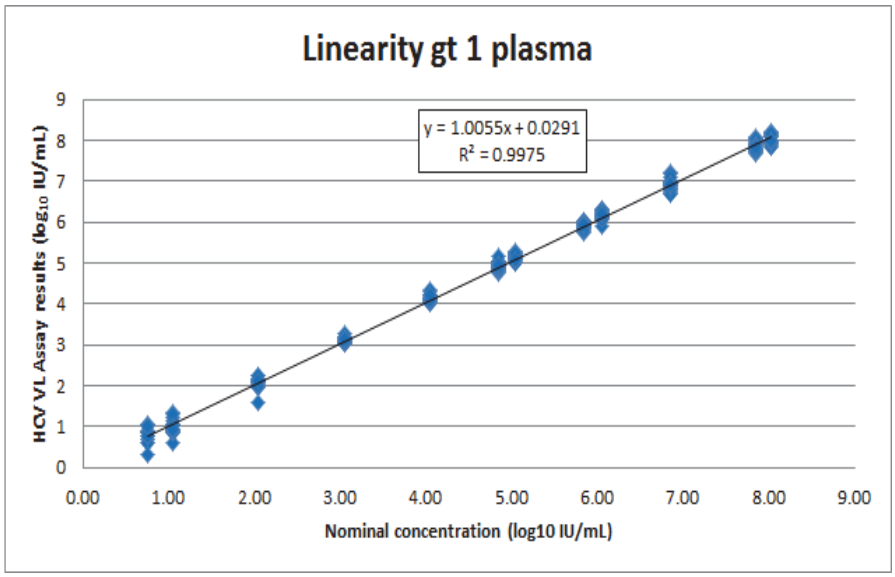


Figure 9. Linearity Genotype 1 in EDTA Plasma for the HCV VL Assay

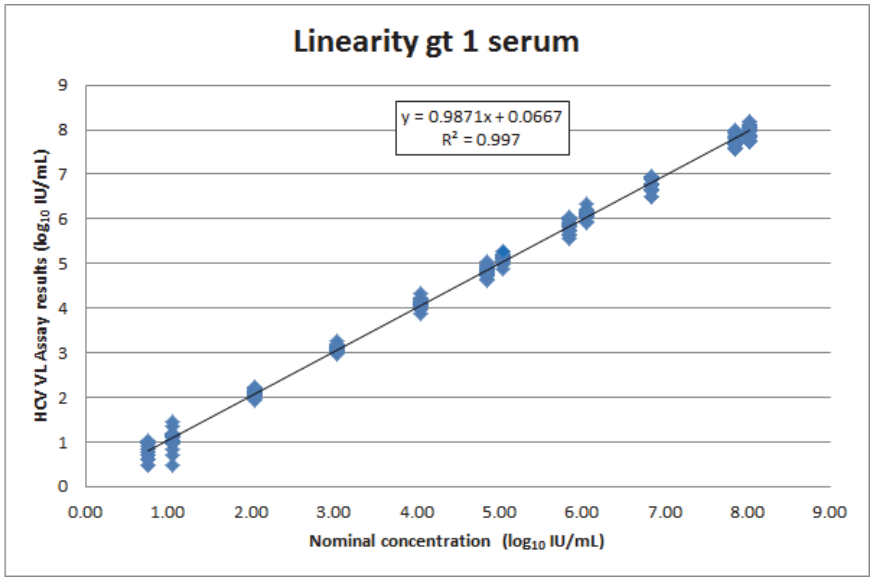


Figure 10. Linearity Genotype 1 in Serum for the HCV VL Assay

To confirm the linear range and evaluate the inclusivity of the HCV VL assay, panels consisting of clinical specimens representing HCV genotype 2 – 6 and Armored RNA® when available (genotypes 2 and 3 only) were prepared in negative human EDTA plasma. 7 – 13 panel members per genotype covering as wide a range as possible, varying from ~ 0.9 – 6 $\log_{10}$ IU/mL for genotype 5 to ~ 0.9 – 8.3 $\log_{10}$ for genotype 3, were prepared and analyzed in replicates of four on each of three testing days using two kit lots. For each genotype, 24 replicates per panel member were tested. The nominal concentrations of the reference materials used were calibrated to the WHO 4th HCV International Standard (06/102). All genotypes responded linearly with R^2 values ranging from 0.994 – 0.998.

18.5 Analytical Specificity (Exclusivity)

The analytical specificity of the HCV VL assay was evaluated by adding potentially cross-reacting organisms at 1 x 10^5 CFU/mL, copies/mL or $TCID_{50}$/mL input concentration into HCV negative EDTA plasma and in plasma that contained ~25 IU/mL HCV reference material (clinical specimen genotype 1). Tested organisms are listed in Table 8.

Table 8. Analytical Specificity Organisms

Human Immunodeficiency virus 1
Human Immunodeficiency virus 2
Human T-cell lymphotropic virus I
Human T-cell lymphotropic virus II
Candida albicans
Cytomegalovirus
Epstein-Barr virus
Hepatitis A virus
Hepatitis B virus
Herpes simplex virus 1
Herpes simplex virus 2
Human herpes virus 6
Human herpes virus 8
Varicella Zoster virus
BK Human polyoma virus
Banzi virus
Ilheus virus
West Nile virus
Zika virus
Human papilloma virus 16
Human papilloma virus 18
Staphylococcus epidermidis
Staphylococcus aureus

None of the tested organisms showed cross reactivity and all positive replicates resulted in concentrations of HCV RNA within ± 0.5 log from a HCV positive control when tested using the HCV VL assay. In addition to the species listed in Table 8, Dengue virus and vaccinia virus were analyzed *in silico* since material representing the viruses could not be obtained for testing. No practical significant sequence similarity was found between the analyzed viruses and the primers and probes of the Xpert HCV VL assay.

18.6 Potentially Interfering Substances

The susceptibility of the HCV VL assay to interference by elevated levels of endogenous substances, by drugs prescribed to HCV infected patients and by autoimmune disease markers was evaluated. HCV negative EDTA plasma and plasma that contained ~25 IU/mL HCV reference material (clinical specimen genotype 1) were tested.

Elevated levels of the endogenous substances listed in Table 9 were shown not to interfere with the quantification of the HCV VL assay or impact the assay specificity.

Table 9. Endogenous Substances and Concentration Tested

Substance	Tested Concentration
Albumin	9 g/dL
Bilirubin	20 mg/dL
Hemoglobin	500 mg/dL
Human DNA	0.4 mg/dL
Triglycerides	3000 mg/dL

The drug components as presented in Table 10 were shown not to interfere with the quantification of the HCV VL assay or impact the assay specificity when tested at three times peak level concentration in five drug pools.

Table 10. Drug Pools Tested

Pool	Drugs
Control	N/A
1	Zidovudine, Saquinavir, Ritonavir, Interferon alfa-2b, Clarithromycin
2	Abacavir sulfate, Fosamperavir Calcium, Peginterferon 2b, Ribavirin
3	Tenofovir disoproxil fumarate, Lamivudine (3TC), Indinavir sulfate, Ganciclovir, Valganciclovir HCl, Acyclovir
4	Stavudine (d4T), Efavirenz, Lopinavir, Enfuvirtide (T-20), Ciprofloxacin
5	Nevirapine, Nelfinavir mesylate, Azithromycin, Valacyclovir HCl

Testing of specimens from ten individuals per autoimmune disease marker shows no interference with the autoimmune disease markers systemic lupus erythematosus (SLE), anti-nuclear antibody (ANA), or rheumatoid factor (RF) using the HCV VL assay.

18.7 Seroconversion Sensitivity

The sensitivity of the HCV VL Assay was evaluated by testing sequential plasma specimens from ten seroconversion panels with a total of 59 panel members. Each seroconversion panel consisted of undiluted plasma specimens collected from a single donor during development of HCV infection and subsequent immune response. The HCV VL assay detected HCV RNA in 51 out of 57 tested specimens with valid test result as compared to 21 of the 59 tested that were detected by at least one of the HCV antibody tests (Abbott ARCHITECT HCV Ab, Abbott PRISM HCV Ab, Ortho® Ver. 3.0 ELISA HCV Ab, Ortho HCV 3.0 ELISA Test System with Enhanced SAVe, Ortho Vitros Eci, Siemens ADIVA Centaur). HCV RNA was detected by the HCV VL Assay prior to antibody tests in nine seroconversion panels and at the same time point for one seroconversion panel. The result is presented in Table 11.

Table 11. Seroconversion Sensitivity of the HCV VL Assay

Panel No	No. of Specimens in Panel	Days Spanned	No. of Reactive Panel Members		Days to First Reactive Result		Days Between First Reactive Result with Xpert HCV VL and Any Ab Test
			Xpert HCV VL	Antibody (Ab) Test[a]	Xpert HCV VL	Antibody (Ab) Test[a]	
PHV913	4	9	4	2	0[b]	7	7
PHV915	4	14	3[c]	2	5[c]	12	7
PHV920	9	35	9	7	0[b]	13	13
PHV922	6	17	5[c]	5	3[c]	3	0
PHV924	6	88	6	3	0[b]	59	59
PHV925	5	27	5	1	0[b]	27	27
PHV926	5	14	5	1	0[b]	14	14
PHV927	5	17	4	0	4	17[d]	13
PHV928	9	50	7	0	29	50[d]	21
PHV929	6	22	3	0	14	22[d]	8

a. Antibody test based on vendor data: Abbott ARCHITECT HCV Ab, Abbott PRISM HCV Ab, Ortho Ver. 3.0 ELISA HCV Ab, Ortho Enhanced SAVe HCV Ab,Ortho Vitros Eci, Siemens ADIVA Centaur.
b. All bleeds were detected with the Xpert HCV VL Assay.
c. All test results of Xpert HCV VL is presented, first panel member caused an invalid test result.
d. All bleeds were non-reactive for HCV Antibodies (based on vendor information). The last bleed day is used as “Days to First Reactive Result”

18.8 Sample Collection Media Equivalence (EDTA, PPT-EDTA and Serum)

For each sample collection media (EDTA, PPT-EDTA and serum) specimens from 50 matched HCV positive individuals and 25 matched HCV negative specimens were collected and tested using one kit lot of the HCV VL assay.

As shown in Figure 11 and Figure 12 equivalent performance of the HCV VL assay was shown for EDTA plasma versus serum samples and EDTA plasma versus PPT-EDTA plasma samples. All HCV positive specimens collected in serum or PPT-EDTA plasma produced concentrations of HCV RNA within ±0.5 $\log_{10}$ IU/mL of the HCV positive specimen collected in EDTA plasma when tested using the HCV VL assay.

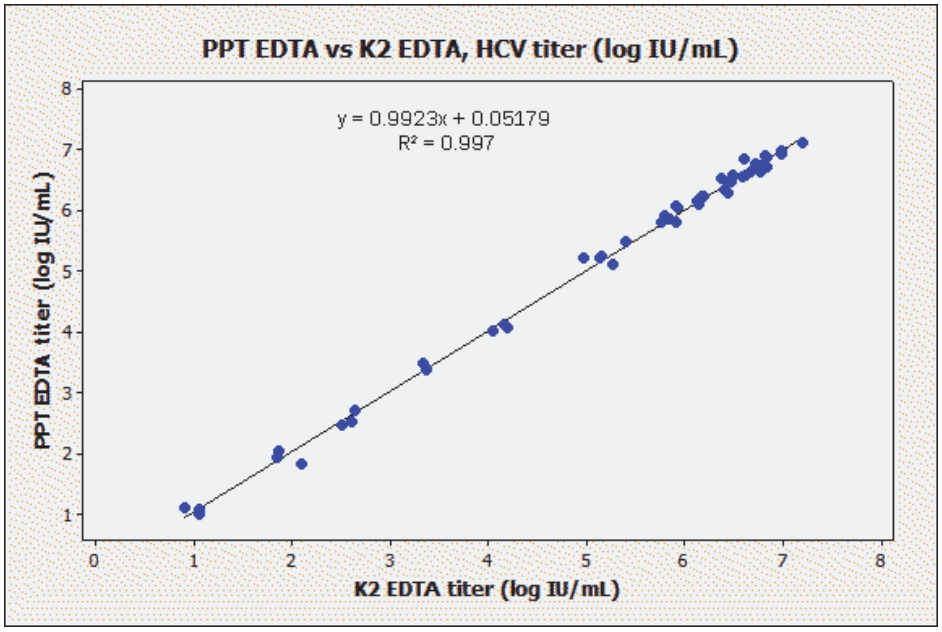


Figure 11. Scatterplot of Log IU/mL PPT-EDTA versus Log IU/mL EDTA

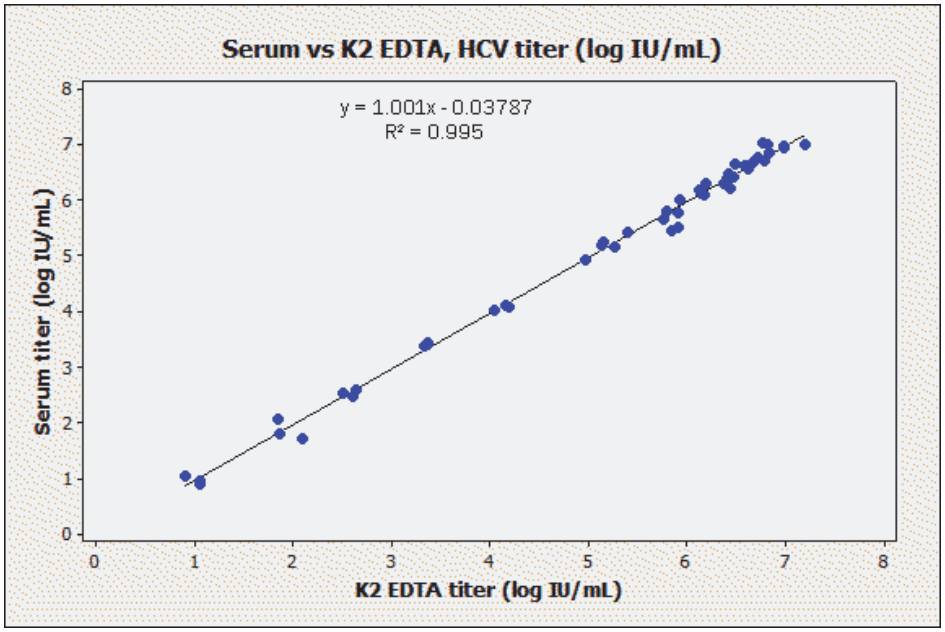


Figure 12. Scatterplot of Log IU/mL Serum versus Log IU/mL EDTA Plasma

19 Performance Characteristics – Clinical Performance

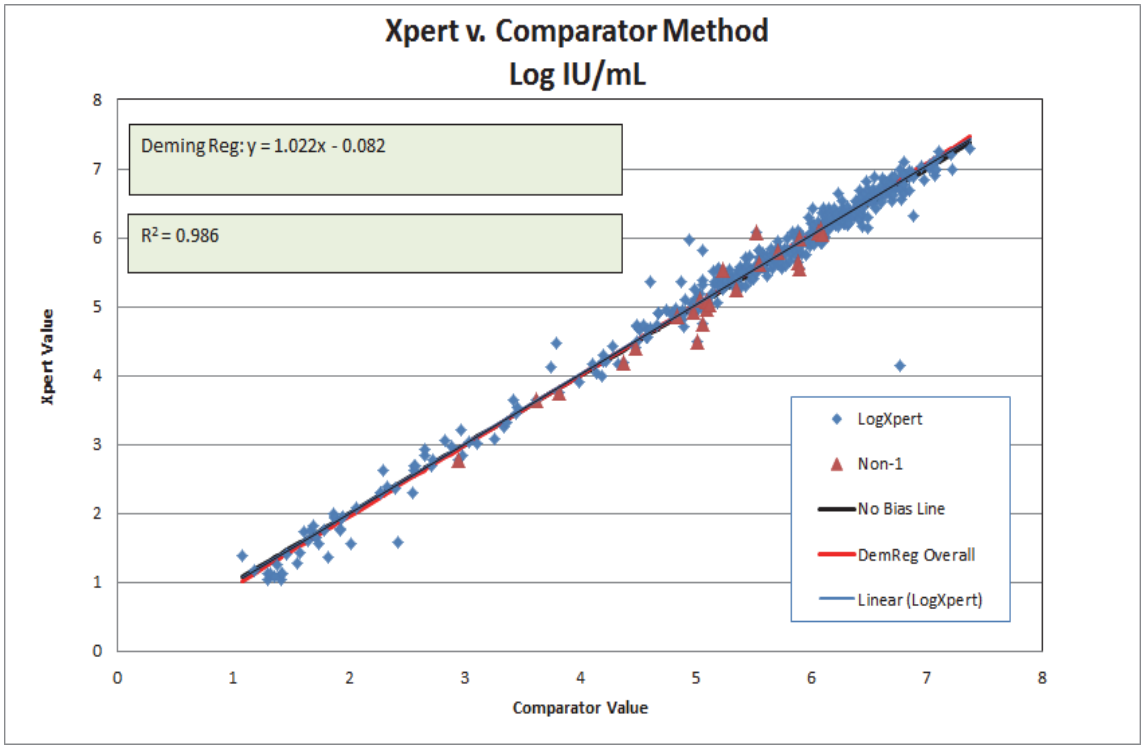
Specificity

The specificity of the HCV VL assay was evaluated using 501 EDTA plasma specimens from HCV negative blood donors. HCV RNA was not detected in any of the 501 specimens tested by the Xpert HCV VL assay demonstrating 100% specificity (95% CI: 99.2-100.0).

Method Correlation

A multi-site study was conducted to evaluate the performance of the HCV VL assay relative to a comparator method using fresh and frozen human plasma or serum specimens collected from HCV infected individuals. Of the 607 eligible specimens, each from unique individuals, 408 (67.2%) were collected from male subjects. The average age was 50.2 ± 13.2 years with an age range of 21 to 86 years.

Of the 607 specimens, 389 were within the quantitation range of both assays including 23 specimens that were HCV non-1 genotypes (2, 2a, 2b, 2c, 3, 3a, 4 & 6) and one mixed genotype (HCV 1 & 6). The Deming regression shows very good correlation between the HCV VL and the comparator method with a slope of 1.022 and intercept of 0.082. The R^2 was 0.986.



*HCV non-1 genotypes are represented as triangles. A single outlier was not included in the analysis.

Figure 13. Xpert v. Comparator Method

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22 Technical Assistance

Before contacting Cepheid Technical Support, collect the following information:

- Product name
- Lot number
- Serial number of the instrument
- Error messages (if any)
- Software version and, if applicable, Computer Service Tag number

Contact Information

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Contact information for all Cepheid Technical Support offices is available on our website: www.cepheid.com/en/CustomerSupport.

23 Table of Symbols

Symbol	Meaning
	Catalog number
	*In vitro* diagnostic medical device
	Do not reuse
	Batch code
	Caution
	Manufacturer
	Country of manufacture
	Contains sufficient for <n> tests
	Control
	Expiration date
	CE marking – European Conformity
	Temperature limitation
	Biological risks
	Warning
	Authorized representative in Switzerland
	Importer

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