REAL WORLD HCV GENOTYPING

Hepatitis C Therapeutic Registry and Research Network

ClinicalTrials.gov Identifier: NCT01474811

UF Clinical and Translational Science Institute
UNIVERSITY of FLORIDA

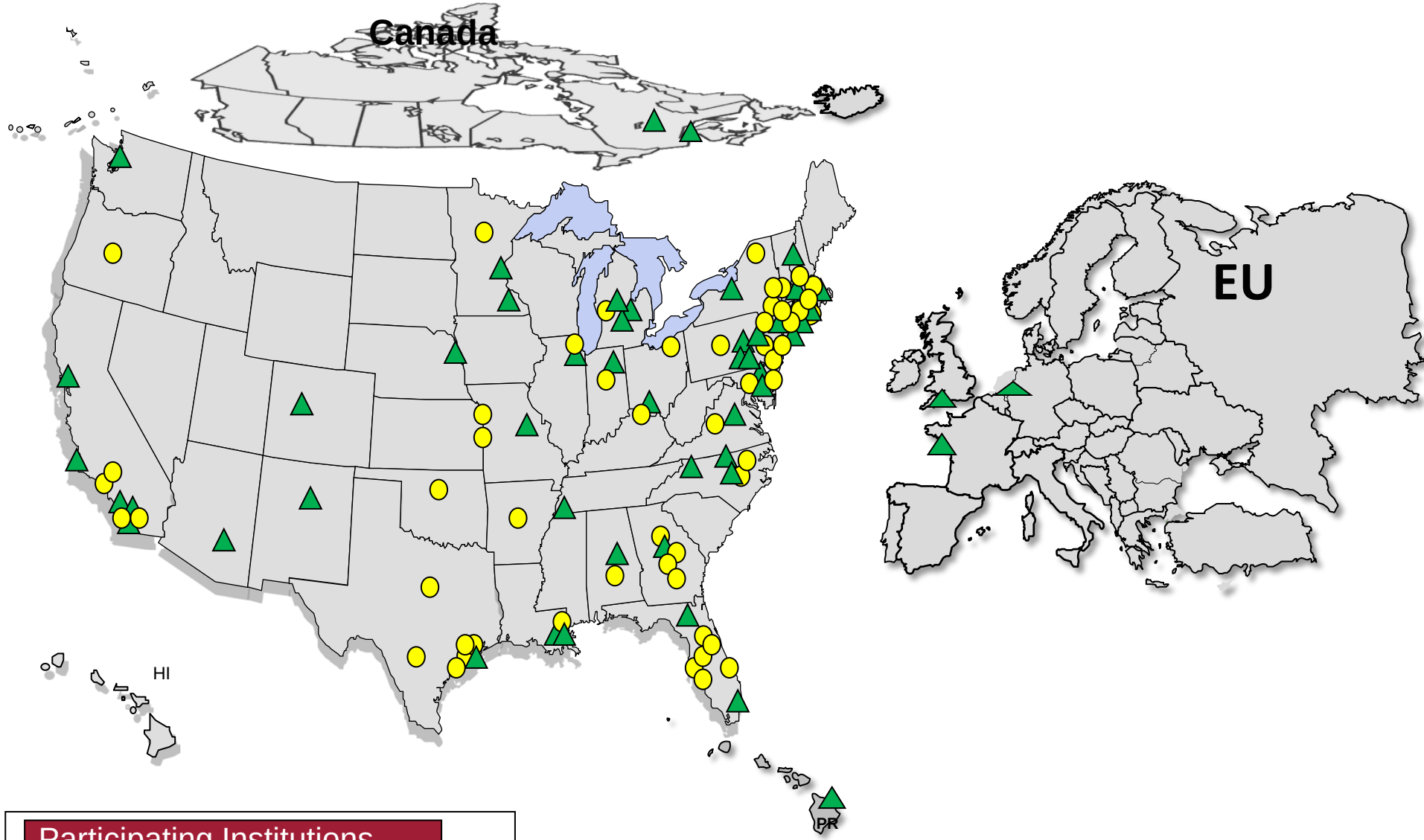
UNC SCHOOL OF MEDICINE

HCV-TARGET

- **Mission: to establish an international registry of patients undergoing treatment with new therapies for HCV at both academic and community practices**
- **Study Design: Longitudinal, observational study**
  - **Inclusion criteria: Adult patients (≥ 18 years) being treated with regimens containing at least one direct acting anti-viral agent.**
  - **Exclusion criteria: Inability to provide informed consent**
- **Specific aims**
  - **Improve information of populations underrepresented in phase III trials**
  - **Identify and remediate educational gaps and adverse event management**
  - **Serve as a core for collaborative, translational studies**
- **Structure**
  - **Clinical coordinating center and biorepository (University of Florida)**
  - **Data coordinating center (University of North Carolina)**
  - **Genentech PegBase USA data integrated in HCV-TARGET**

HCV TARGET

HCV-TARGET: An International Consortium

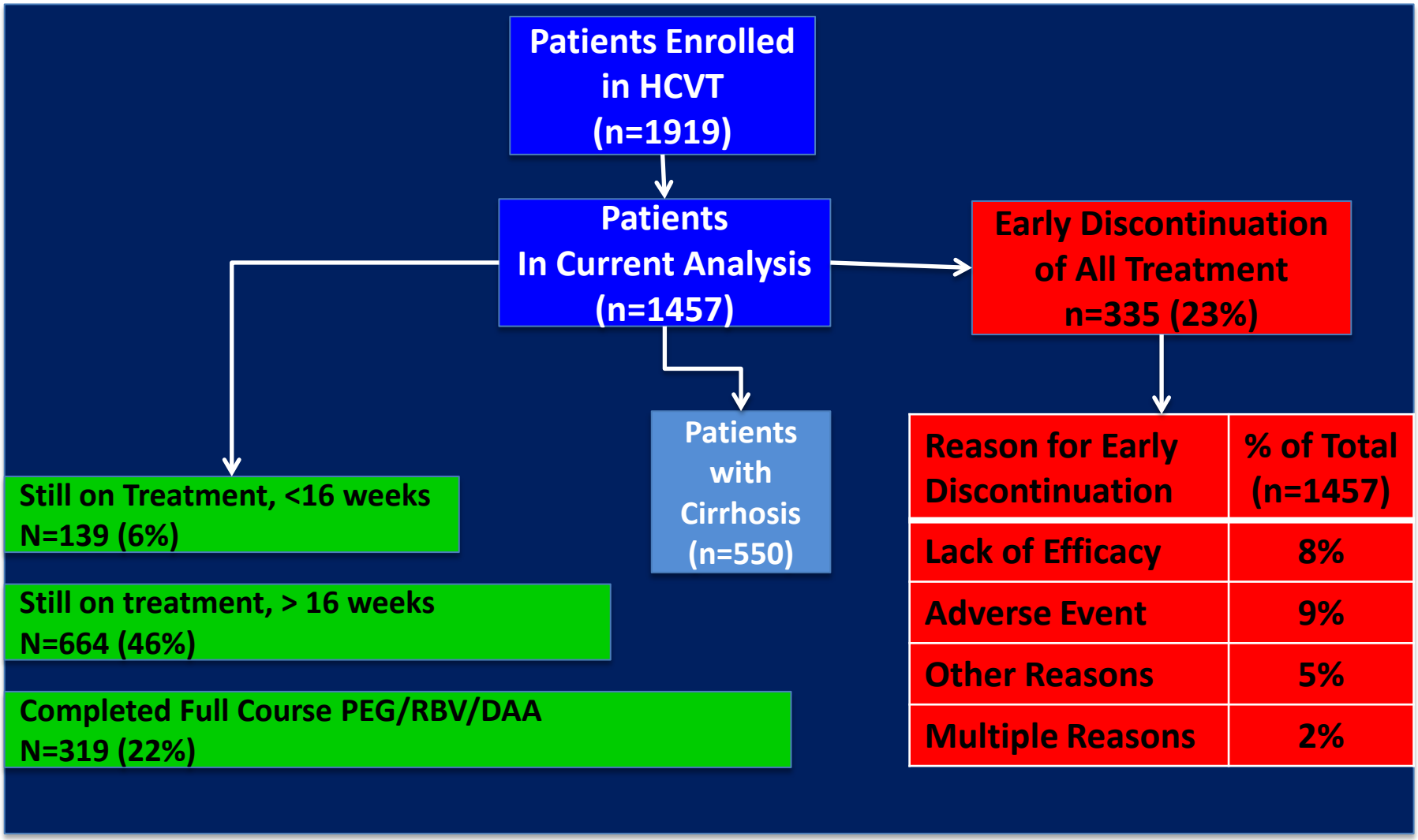


Participating Institutions

- **Academic Site- 44**
- **Community Site- 59**

HCV-TARGET

Patient Disposition



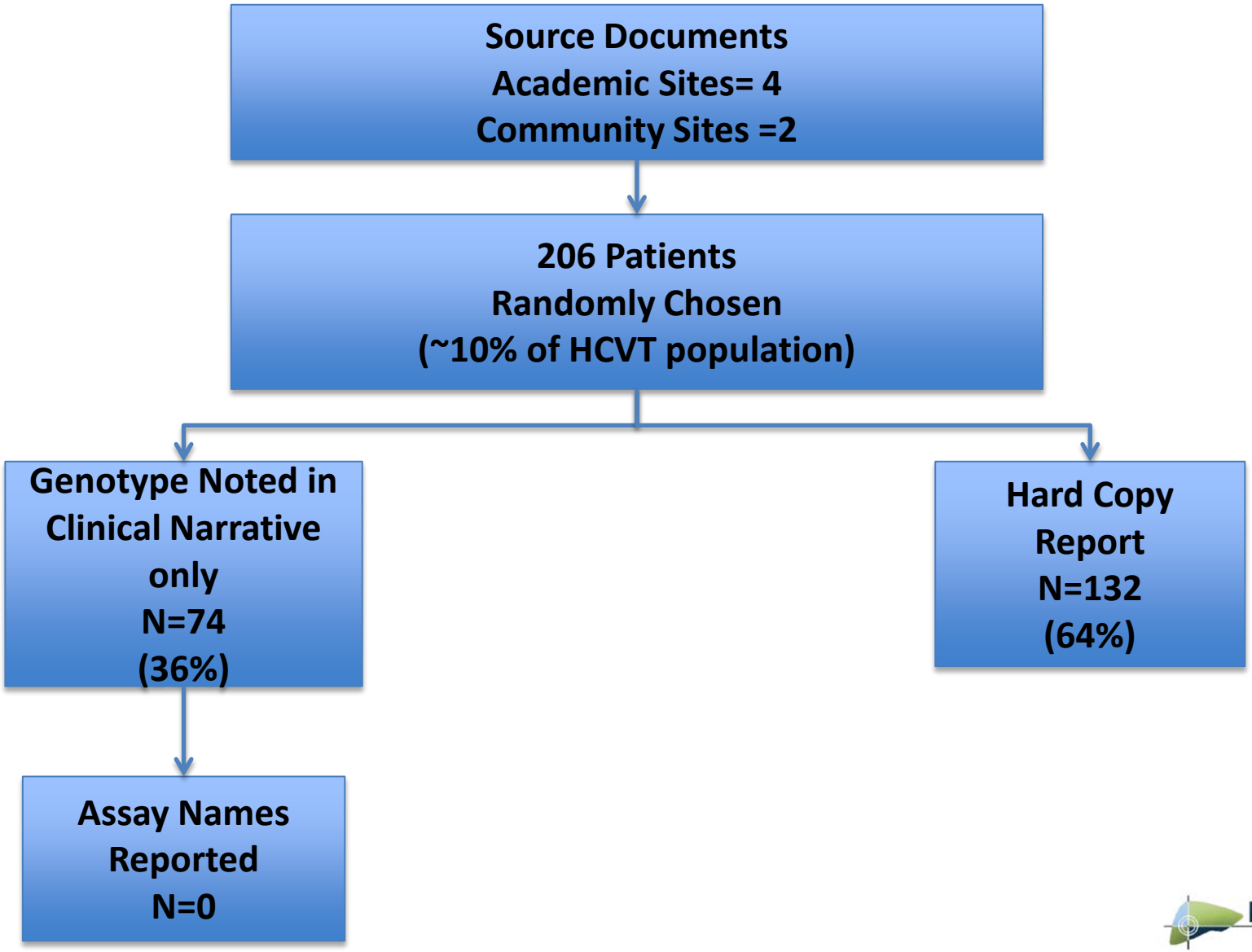
Characteristics	Total (n= 1457)	Telaprevir (n=1079)	Boceprevir (n=342)
Age, years (Mean)	62 years	59.5 years	67.1 years
18-39 years (n,%)	123 (8%)	92 (9%)	31 (9%)
40-64 years	1160 (80%)	887 (82%)	270 (79%)
65 and older	104 (7%)	73 (7%)	31 (9%)
Gender: Male/Female	60%/40%	60%/40%	62%/38%
BMI	29.4	29.7	28.8
Race or Ethnicity			
Caucasian	1056 (72%)	790 (73%)	245 (72%)
African-American	300 (21%)	223 (21%)	72 (21%)
Asian	22 (2%)	16 (1%)	6 (2%)
Hispanic	95 (7%)	76 (7%)	18 (5%)
HCV Genotype			
1a	842 (58%)	639 (59%)	192 (56%)
1b	283 (19%)	207 (19%)	70 (20%)
1 (No subtype)	204 (14%)	152 (14%)	45 (13%)
2,3,4	16 (1%)	11 (1%)	4 (1%)
Cirrhosis	550 (38%)	437 (41%)	106 (31%)
Prior treatment status			
Naïve	720 (49%)	526 (49%)	182 (53%)
Treatment Experience	714 (49%)	547 (51%)	154 (45%)

HCV-Genotyping in HCV-TARGET

- **HCV-TARGET utilizes a standardized, centralized source data abstraction core to abstract HCV treatment data from de-identified clinical medical records provided from participating sites**
- **Thus, all source documents from participating patients are available for review**
- **Retrospective review of available genotyping data performed in a sample of HCVT patients**

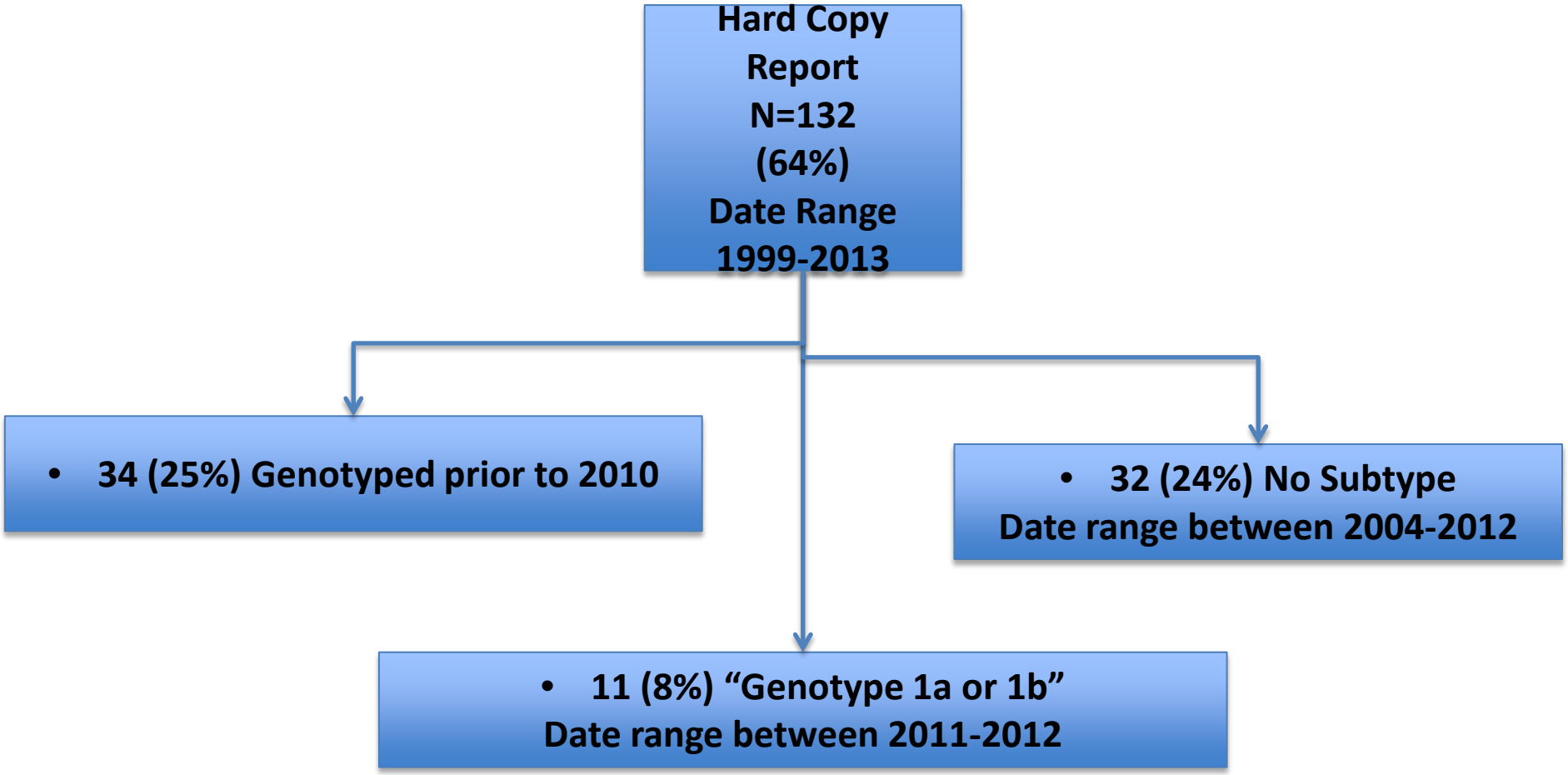
HCV-TARGET

HCV Genotyping in HCV-TARGET



HCV-TARGET

HCV-Genotyping in HCV-TARGET



HCV-TARGET

HCV-Genotyping in HCV-TARGET

Assays

- Specific assay names were identified in only 27% of the reports (Versant, Invader TWT, Genosure)
- Where HCV Genotype is identified in the clinical narratives, assay names are not included
- HCV reports provided from clinical trials do not provide the specific assay names

Testing Laboratories

- 66% of patients had HCV Genotyping resulted from QUEST, LabCorp, or ARUP
  - 1% indicated the Genotype Assay Name/Version used

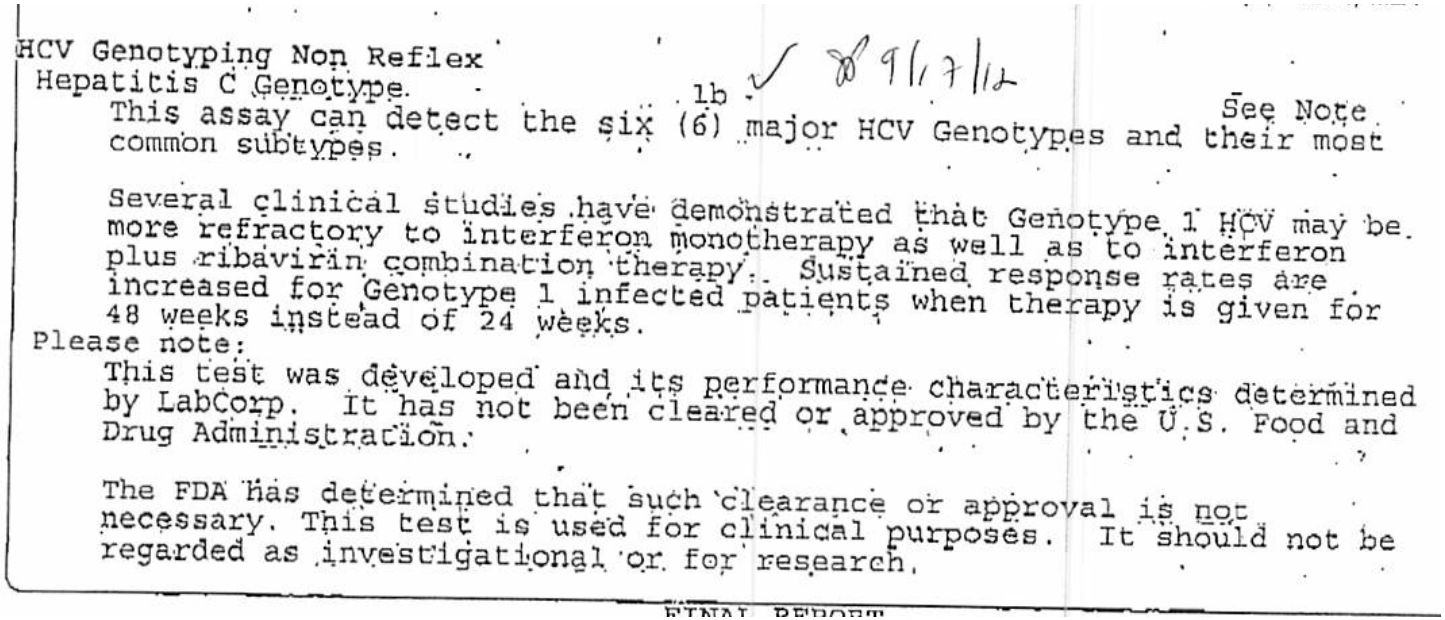
Lab	Methodology
ARUP	*Dye-Terminator Chem (ABI)*
LabCorp	*Not specified on reports*
QUEST	*LiPA, Assay Name not given*

HCV-TARGET

REAL-WORLD REPORTS

HCV TARGET

LABCORP



HCV Genotyping Non Reflex
Hepatitis C Genotype. 1b ✓ 9/17/12

This assay can detect the six (6) major HCV Genotypes and their most common subtypes. See Note

Several clinical studies have demonstrated that Genotype 1 HCV may be more refractory to interferon monotherapy as well as to interferon plus ribavirin combination therapy. Sustained response rates are increased for Genotype 1 infected patients when therapy is given for 48 weeks instead of 24 weeks.

Please note:

This test was developed and its performance characteristics determined by LabCorp. It has not been cleared or approved by the U.S. Food and Drug Administration.

The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational or for research.

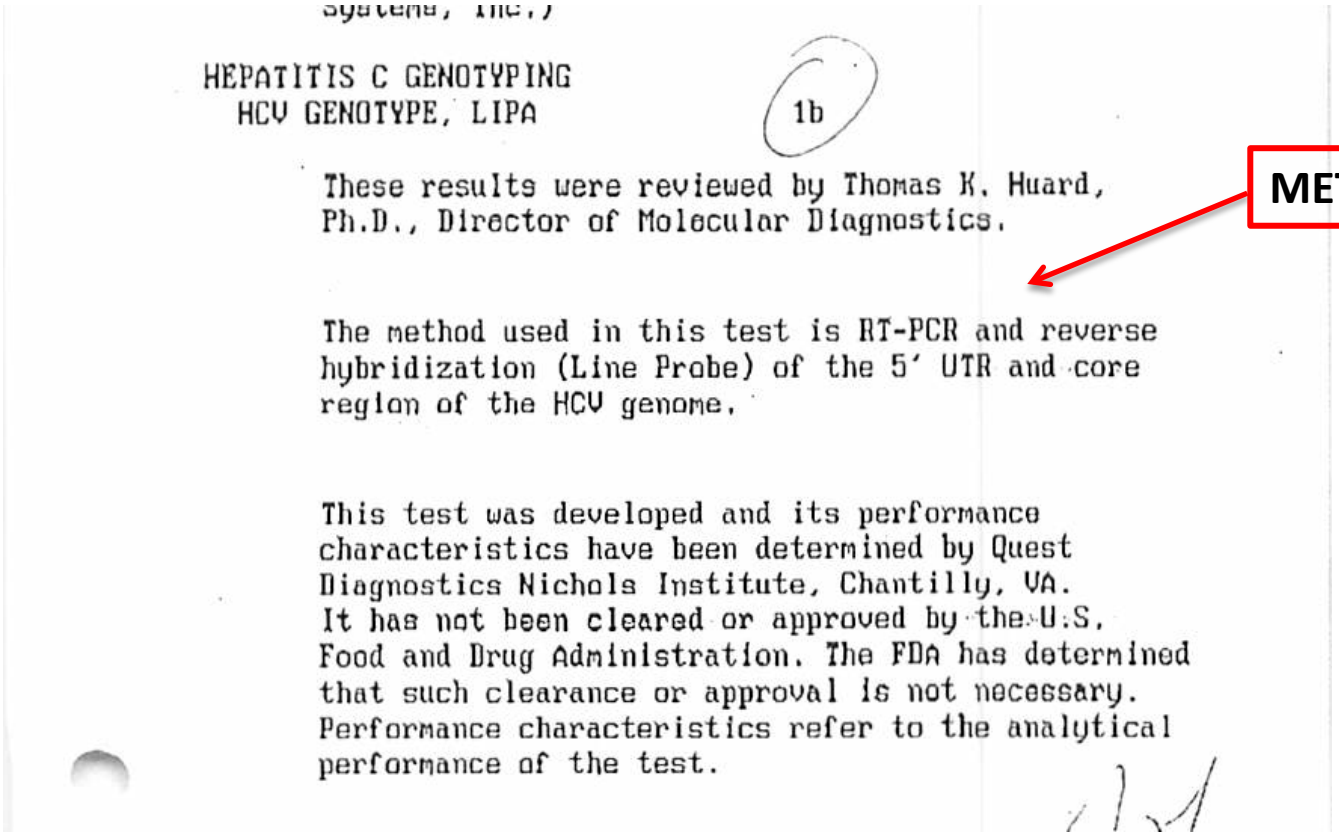
FINAL REPORT

ASSAY and METHODOLOGY NOT SPECIFIED

2011

HCV TARGET

QUEST- 2010



Systems, Inc.)

HEPATITIS C GENOTYPING
HCV GENOTYPE, LIPA 1b

These results were reviewed by Thomas K. Huard, Ph.D., Director of Molecular Diagnostics.

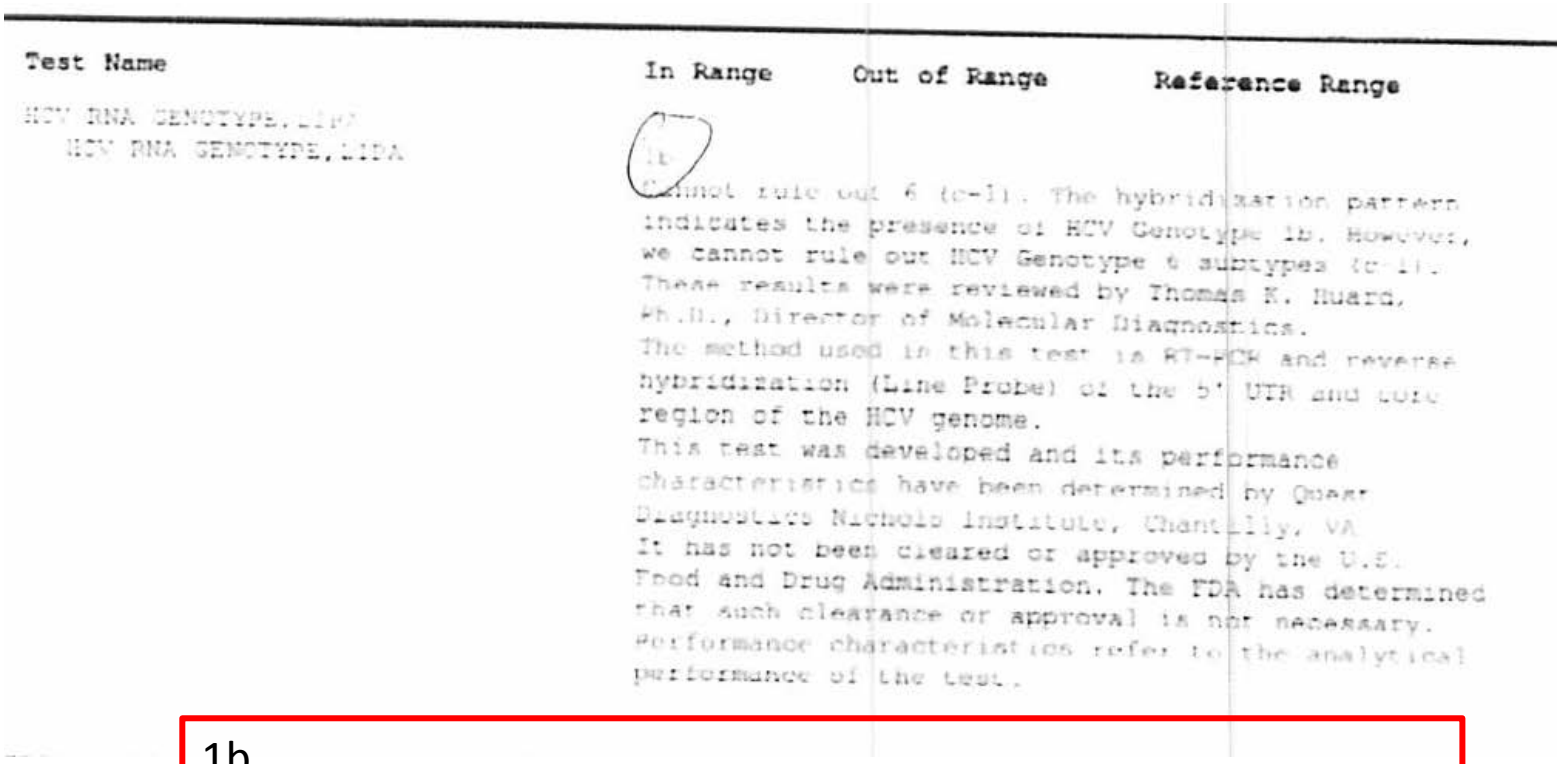
The method used in this test is RT-PCR and reverse hybridization (Line Probe) of the 5' UTR and core region of the HCV genome.

This test was developed and its performance characteristics have been determined by Quest Diagnostics Nichols Institute, Chantilly, VA. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Performance characteristics refer to the analytical performance of the test.

METHODOLOGY SPECIFIED

2010

QUEST-2011



Test Name	In Range	Out of Range	Reference Range
HCV RNA GENOTYPE,LIPA HCV RNA GENOTYPE,LIPA	1b		

Cannot rule out 6 (c-1). The hybridization pattern indicates the presence of HCV Genotype 1b. However, we cannot rule out HCV Genotype 6 subtypes (c-1). These results were reviewed by Thomas K. Ruark, Ph.D., Director of Molecular Diagnostics. The method used in this test is RT-PCR and reverse hybridization (Line Probe) of the 5' UTR and core region of the HCV genome. This test was developed and its performance characteristics have been determined by Quest Diagnostics Nichols Institute, Chantilly, VA. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Performance characteristics refer to the analytical performance of the test.

2011

1b
Cannot rule out 6 (c-1). The hybridization pattern indicates the Presence of HCV Genotype 1b. However, we cannot rule out HCV Genotype 6 (c-1)

HCV TARGET

QUEST-2012

Entry Date
5/29/2012

Component Results

Component	Collected
HCV Genotype	05/25/2012
1a	

Comment:

These results were reviewed by Thomas K. Huard, Ph.D., Director of Molecular Diagnostics.

The AccuType(R) IL28B test can help stratify HCV-infected individuals into those who are predisposed to respond more favorably and those who are predisposed to respond less favorably to standard HCV therapy. A favorable IL28B genotype (ie, CC) predicts improved treatment response for individuals infected with HCV genotype 1.
Reference: Clin Gastroenterol Hepatol. 2011;9:344-350.
To order the IL-28B test please submit a new whole blood sample for test code 90251.

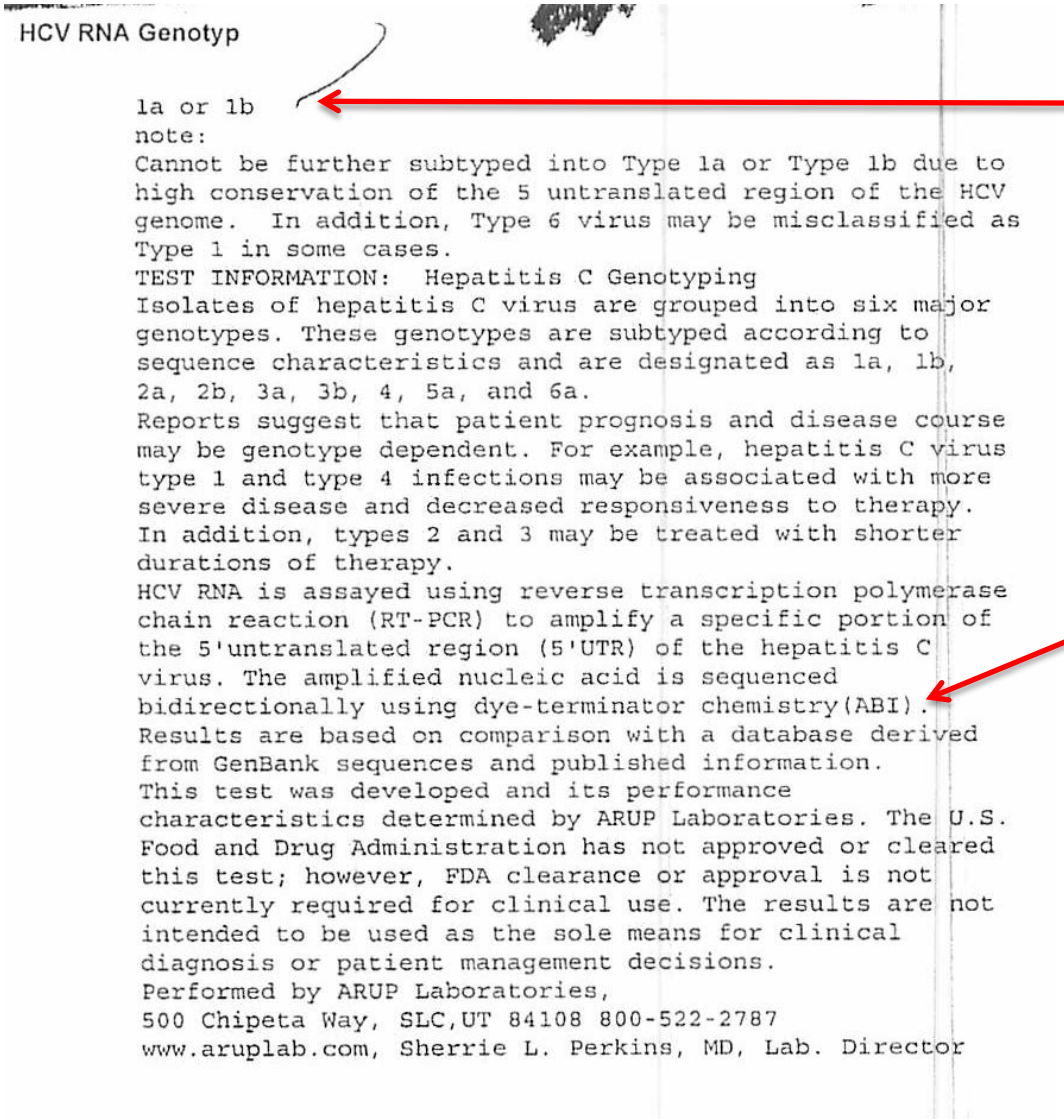
The method used in this test is RT-PCR and reverse hybridization (Line Probe) of the 5' UTR and core region of the HCV genome.

This test was developed and its performance characteristics have been determined by Quest Diagnostics Nichols Institute, Chantilly, VA. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Performance characteristics refer to the analytical performance of the test.

METHODOLOGY SPECIFIED,

HCV TARGET

ARUP



HCV RNA Genotyp

1a or 1b
note:
Cannot be further subtyped into Type 1a or Type 1b due to high conservation of the 5 untranslated region of the HCV genome. In addition, Type 6 virus may be misclassified as Type 1 in some cases.
TEST INFORMATION: Hepatitis C Genotyping
Isolates of hepatitis C virus are grouped into six major genotypes. These genotypes are subtyped according to sequence characteristics and are designated as 1a, 1b, 2a, 2b, 3a, 3b, 4, 5a, and 6a.
Reports suggest that patient prognosis and disease course may be genotype dependent. For example, hepatitis C virus type 1 and type 4 infections may be associated with more severe disease and decreased responsiveness to therapy. In addition, types 2 and 3 may be treated with shorter durations of therapy.
HCV RNA is assayed using reverse transcription polymerase chain reaction (RT-PCR) to amplify a specific portion of the 5'untranslated region (5'UTR) of the hepatitis C virus. The amplified nucleic acid is sequenced bidirectionally using dye-terminator chemistry(ABI).
Results are based on comparison with a database derived from GenBank sequences and published information.
This test was developed and its performance characteristics determined by ARUP Laboratories. The U.S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions.
Performed by ARUP Laboratories,
500 Chipeta Way, SLC,UT 84108 800-522-2787
www.aruplab.com, Sherrie L. Perkins, MD, Lab. Director

Cannot determine HCV subtype

2011

METHODOLOGY SPECIFIED, ASSAY NOT SPECIFIED

HCV TARGET

CPL

HEPATITIS C GENOTYPE
HCV Genotyping<a>

• 1a

HCV RNA is analyzed using reverse transcriptase amplification (RT-PCR) and differential hybridization of the 5'UTR and core regions of the HCV genome. The Versant HCV Amplification (LiPA) 2.0 analyte specific reagent is utilized. Possible genotypes include 1, 1a, 1b, 2, 2a/2c, 2b, 3, 3a, 3b, 3c, 3k, 4, 4a/4c/4d, 4b, 4e, 4f, 4h, 5a, 6a/6b, 6c-l.

This test uses analyte specific reagents and its performance characteristics were determined by CPL. It has not been cleared by the U.S. Food and Drug Administration (FDA), but the FDA has determined that such clearance is not necessary. This test is not to be regarded as investigational or for research only.

CPL is certified to perform high complexity testing under the Clinical Laboratory Improvement Amendments of 1988.

SPECIFIES ASSAY AND METHODOLOGY

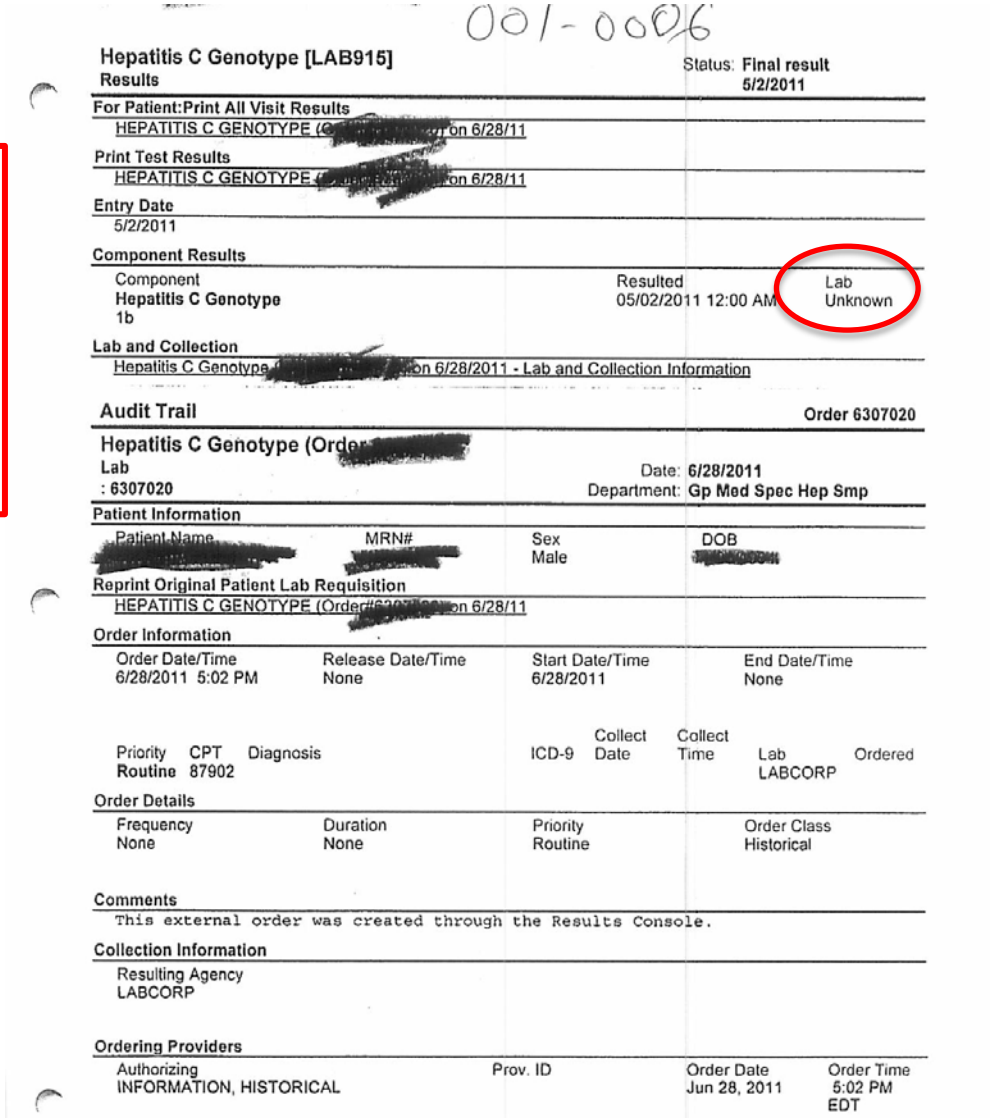
2011

HCV TARGET

Local Report from EMR

METHODOLOGY NOT SPECIFIED, ASSAY NOT SPECIFIED

Result transcribed into EMR by center staff without assay name or methodology



001-0096

Hepatitis C Genotype [LAB915]
Results

Status: **Final result**
5/2/2011

For Patient:Print All Visit Results
HEPATITIS C GENOTYPE (...on 6/28/11

Print Test Results
HEPATITIS C GENOTYPE (...on 6/28/11

Entry Date
5/2/2011

Component Results

Component	Resulted	Lab
Hepatitis C Genotype 1b	05/02/2011 12:00 AM	Unknown

Lab and Collection
Hepatitis C Genotype (...on 6/28/2011 - Lab and Collection Information

Audit Trail — **Order 6307020**

Hepatitis C Genotype (Order...

Lab : 6307020

Date: **6/28/2011**
Department: **Gp Med Spec Hep Smp**

Patient Information

Patient Name	MRN#	Sex	DOB
[redacted]	[redacted]	Male	[redacted]

Reprint Original Patient Lab Requisition
HEPATITIS C GENOTYPE (Order#...on 6/28/11

Order Information

Order Date/Time	Release Date/Time	Start Date/Time	End Date/Time
6/28/2011 5:02 PM	None	6/28/2011	None

Priority	CPT	Diagnosis	ICD-9	Collect Date	Collect Time	Lab	Ordered
Routine	87902					LABCORP	

Order Details

Frequency	Duration	Priority	Order Class
None	None	Routine	Historical

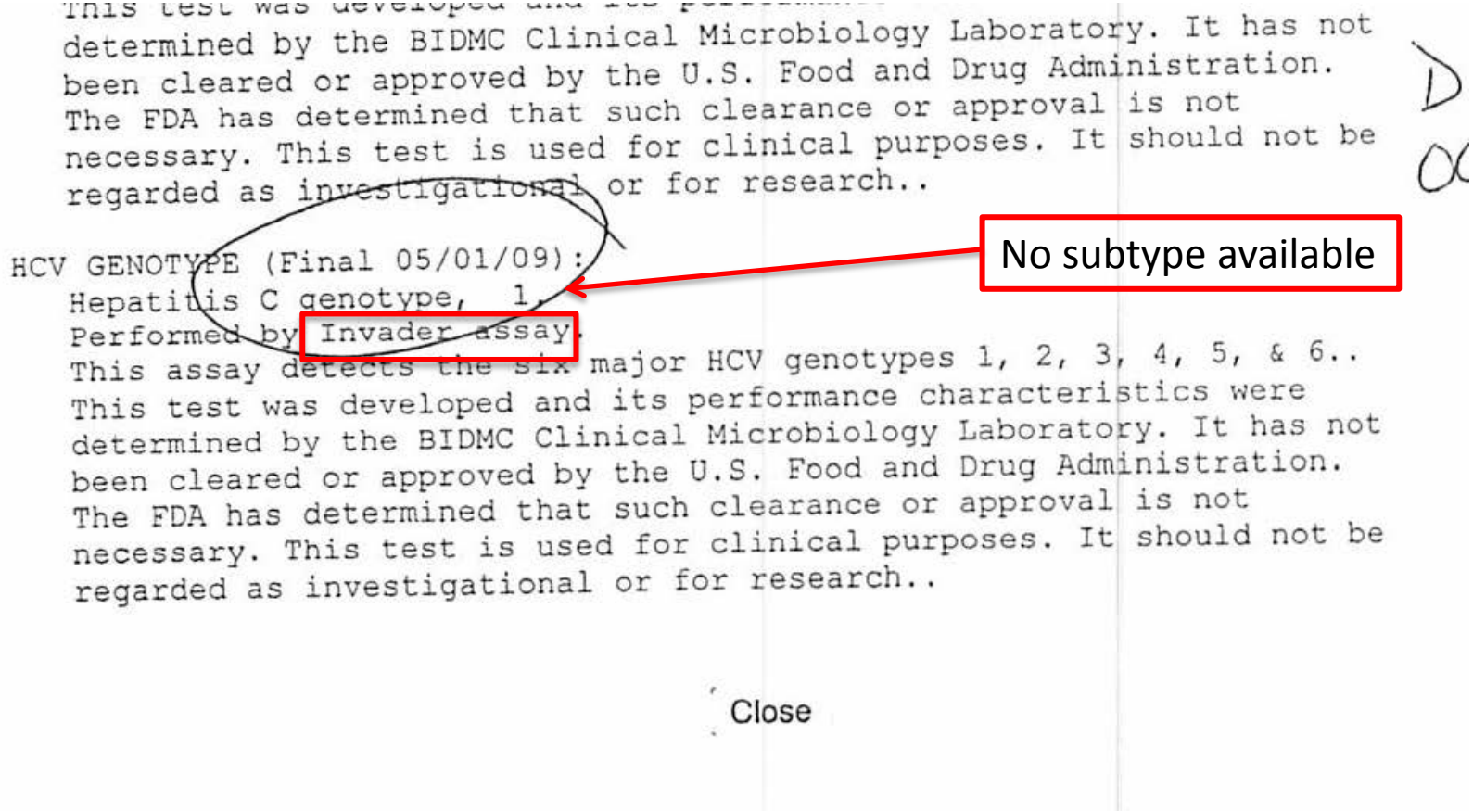
Comments
This external order was created through the Results Console.

Collection Information
Resulting Agency
LABCORP

Ordering Providers

Authorizing	Prov. ID	Order Date	Order Time
INFORMATION, HISTORICAL		Jun 28, 2011	5:02 PM EDT

Local Lab (Academic Center)



This test was developed and its performance
determined by the BIDMC Clinical Microbiology Laboratory. It has not
been cleared or approved by the U.S. Food and Drug Administration.
The FDA has determined that such clearance or approval is not
necessary. This test is used for clinical purposes. It should not be
regarded as investigational or for research..

HCV GENOTYPE (Final 05/01/09):
Hepatitis C genotype, 1.
Performed by Invader assay.
This assay detects the six major HCV genotypes 1, 2, 3, 4, 5, & 6..
This test was developed and its performance characteristics were
determined by the BIDMC Clinical Microbiology Laboratory. It has not
been cleared or approved by the U.S. Food and Drug Administration.
The FDA has determined that such clearance or approval is not
necessary. This test is used for clinical purposes. It should not be
regarded as investigational or for research..

Close

No subtype available

2009

ASSAY SPECIFIED BUT SUBTYPE NOT AVAILABLE

HCV TARGET

MPL- 2009

Component Results	
HEPC GENOTYPING RESU	1 Method: The Hepatitis C Virus (HCV) genotype was determined by the Invader HCV Genotyping Assay v1.0 (Third Wave Technologies). This assay analyzes sequences in the 5' untranslated region of the HCV genome. Subtype information is not provided for because the Invader HCV Genotyping assay cannot distinguish between subtypes. Please call the Molecular Pathology Laboratory (215-662-6121) if you have any questions. Reference: Chen and Weck. (2002). J.Clin.Microbiol. 40(9):3127-3134. NOTE: This test was developed and its performance characteristics determined by the Molecular Pathology Laboratory in the Department of Pathology and Laboratory Medicine at the Hospital of the University of Pennsylvania. This test has not been approved or cleared by the FDA.

ASSAY SPECIFIED BUT THIS ASSAY CANNOT PROVIDE SUBTYPE

HCV TARGET

MPL- 2012

INDICATION FOR TESTING: Determination of hepatitis C (HCV) genotype for prognosis and therapeutic decision-making.

INTERPRETATION: The HCV genotype and subtype was determined and the type(s) detected is indicated above.

CLINICAL SIGNIFICANCE: HCV is a heterogeneous virus that is classified by phylogenetic analysis into six genotypes, each with 1 or more subtypes. Genotypes 1 and 2 are the most commonly encountered in the U.S. population. Genotype 2 and 3 infections have a better response to treatment with pegylated interferon and ribavirin compared to other genotypes. As a result, treatment duration recommendations are typically based on genotype information. [1,2] Protease inhibitors (i.e. boceprevir and telaprevir) are approved only for use in genotype 1 infections in combination with pegylated interferon and ribavirin. In contrast to viral genotype, the clinical utility of HCV viral subtype information is limited.

METHOD: HCV RNA was isolated from plasma using Qiamp QIP Viral RNA Mini kit. The HCV genotype and subtype was determined using hybridization of a biotinylated PCR amplified product to a linear probe array containing 24 immobilized probes spanning the 5' untranslated region and the core region of the HCV genome. (Versant HCV Genotype 2.0 Assay (LiPA), Siemens). The hybridized bands are detected by a streptavidin conjugate and the genotype is determined by the pattern of bands. The assay identifies all 6 HCV genotypes and more than 10 different subtypes. An HCV viral load of at least 125 IU/mL is required for genotyping.

ASSAY LIMITATIONS: This assay may have a limited ability to detect a mixed infection if one genotype/subtype is present at a lower copy number than the main virus genotype/subtype. Some subtypes are not distinguishable by this assay.

REFERENCES

1. Ghany, Mark G., Nelson, David R., et al. An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection: 2011 Practice Guidelines by the American Association for the Study of Liver Diseases. Hepatology 2011; 54: 1433.
2. Ghany MG, Strader DB, Thomas DL, et al: Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335.

This test was developed and its performance characteristics determined by the Molecular Pathology Laboratory in the Department of Pathology and Laboratory Medicine at the Hospital of the University of Pennsylvania. If you have any questions regarding this test please call the Molecular Pathology Laboratory at 215-662-6121 or page the Molecular Pathology resident at 215-980-9868. *** End of report (HV) ***

SPECIFIES ASSAY (VERSANT 2.0) & METHODOLOGY

2012
GENO 1A

HCV TARGET

RETEST CHALLENGES WITH CURRENT ASSAYS

Genotype Result 2006

020-1075

Results	HEPC GENOTYPING [C3510166] (Order 9653629) - Reflex for Order 9502038
Result Information	
Status	
Final result (12/6/2006 3:29 PM)	
Entry Date	
12/6/2006	
Component Results	
HEPC GENOTYPING RESU	1
HEPC GENOTYPING INTE	
HEPC GENOTYPING INTE	
HEPC GENOTYPING INTE	
HEPC GENOTYPING INTE	Method: The HCV genotype was determined by the Invader HCV Genotyping Assay
HEPC GENOTYPING INTE	v1.0 (Third Wave Technologies). This assay analyzes sequences in the 5'
HEPC GENOTYPING INTE	untranslated region of the virus genome. Subtype information is not provided
HEPC GENOTYPING INTE	for because the Invader HCV Genotyping assay cannot distinguish between
HEPC GENOTYPING INTE	subtypes. Reference: Chen and Weck. (2002). J.Clin.Microbiol.

No Subtype

Center Retests Genotype in 2011

020-1075

Results	HEPATITIS C GENOTYPE [HCVGENO] (Order 52737240) - Reflex for Order 524349
R	
R	
R	
Status	
Final result (12/26/2011 2:40 PM)	
Entry Date	
12/26/2011	
Component Results	
HEPATITIS C GENOTYPE	1a or 1b

No Subtype

Comment:
Cannot be further subtyped into Type 1a or Type 1b due to high conservation of the 5 untranslated region of the HCV genome. In addition, Type 6 virus may be misclassified as Type 1 in some cases.
TEST INFORMATION: Hepatitis C Genotyping
Isolates of hepatitis C virus are grouped into six major genotypes. These genotypes are subtyped according to sequence characteristics and are designated as 1a, 1b, 2a, 2b, 3a, 3b, 4, 5a, and 6a.
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This test was developed and its performance characteristics determined by ARUP Laboratories. The U.S

HCV-TARGET

HCV Genotyping
SUMMARY & IMPLICATIONS

- **>1/3 Clinical centers are relying on HCV Genotype information from clinical notes transcribed over time.**
  - **35% of those do not indicate HCV Genotype Subtype**
- **Specific assay information is available for only 17% of HCV Genotypes (hardcopy reports- 35%, clinical notes- 0%)**
- **The most commonly used laboratories in the US do not provide adequate information about HCV Genotype Assaying on HCV Genotype reports**
  - **Laboratory reporting techniques should be revised**
  - **Provider education on methodology is necessary**
- **There are important implications as genotype specific and genotype-preferred therapeutic regimens become available**
  - **Many patients will require HCV Genotype retesting when HCV genotype subtype is of clinical significance to selecting a treatment regimen**

HCV-TARGET

ACKNOWLEDGEMENTS

We thank the study staff, nurses, NP-PA providers, physicians and patients at each study center for their contributions to this work.

Univ of Florida	**Nelson**
UNC	**Fried**
SLU	**Di Bisceglie**
Scripps	**Pockros**
Colorado	**Everson**
Cincinnati	**Sherman**
Univ of Chicago	**Aronsohn/Reau**
Harvard	**Afdhal**
Indiana	**Kwo**
Puerto Rico	**Rodriquez-Torres**
Duke	**Muir**
Umass	**Szabo**
Virginia	**Sterling**
Miami	**Schiff**
Johns Hopkins	**Sulkowski**
University of Paris- FRANCE	**Marcellin**
Royal Free Hospital- UK	**Dusheiko**
Partners in Internal Medicine, PC	**Abraham**
Liver Associates of Texas, PA	**Ankoma-Sey**
University of Virginia Health System	**Argo**
Tri-State Gastroenterology Associates	**Jones**
Ochsner Clinic Foundation	**Joshi**
Fletcher Allen Health Care, Inc.	**Lidofsky**
Litchfield County Gastroenterology	**Lindenberg**
Bend Memorial Clinic	**Lutz**
Mercy Medical Center	**Maheshwari**
Boice-Willis Clinic,PA	**Mah'moud**
University of Rochester	**Maliakkal**
Clinical Research Consultants, Inc.	**Marks**
HMRI Liver Center	**Mena**
New York Methodist Hospital	**Mohanty**
Methodist Transplant Physicians	**Mubarak**
Center for Advanced Gastroenterology PLLC	**Mushahwar**
Wayne State University Physician Group	**Mutchnick**
Methodist Healthcare University Hospital	**Nair**
Yale	**Lim**
AshevilleGastro	**Beavers**
Cornell	**Jacobson**
U Penn	**Reddy**
UCSD	**Kuo**
UCLA	**Saab**
Henry Ford	**Gordon**
Emory University	**Spivey**
Univ of Michigan	**LOK**
Atlanta Med Ctr	**Pearlman**
The Methodist Hospital, Houston, Texas	**Galati**
Mayo- Rochester	**Charlton**
Mayo- AZ	**Vargas**
Orlando Immunology Center	**Hinestrosa**
Virginia Mason	**Kowdley**
Wilmington Gastro	**Meyer**
Tulane University Health Science Center	**Balart**
DeKalb Gastroenterology Associates, LLC	**Balistreri**
Florida Center for Gastroenterology	**Berman**
North Shore University Hospital	**Bernstein**
Kansas City VA Medical Center	**Pandya**
Temple University Hospital	**Patel**
South Bay Gastroenterology	**Piken**
Indianapolis Gastroenterolgy Research Foundation	**Pound**
Mountain View Medical	**Ramani**
Atlanta Center for Gastroenterology PC	**Rausher**
Digestive and Liver Disease Consultants, PA	**Reddy**
Saint Luke's Liver Disease and Transplant Specialists	**Regenstein**
Atlantic Gastroenterology Associates	**Santoro**
Gastroenterology Associates of Central Georgia, LLC	**Sedghi**
DuBois Regional Medical Center	**Stainbrook**
Commonwealth Clinical Studies	**Stone**
Concorde Medical Group PLLC	**Tobias**
Daniel Warner Consultative Medicine	**Warner**
HRH Care	**Kerr**
Metropolitan Research	**Rustgi**
University of Minn	**Hassan**
MNGasto	**Coleman Smith**
Lake Shore Gastro- Chicago community	**O'Riordan**
Liver Instiute of Virginia/Bon Secours	**Shiffman**
UCSF	**Terrault**
Austin Hepatitis Center	**Imitaz Alam**
Toronto Western Hospital Liver Center	**Feld**
Baptist Medical Center-Oklahoma	**Elbeshbeshy**
University of Ottawa	**Cooper**
University of Nebraska	**Mailliard**
Hanover Medical School- GERMANY	**Manns**
Digestive Disease Associates-Maryland	**Ravendhran**
Mass General	**Ray Chung**
Maryland	**Howell**
UAB Gastrology and Hepatology	**Bloomer**
New Orleans Research Institute	**Catinis**
Gastroenterology Associates of Western Michigan, P.L.C.	**Coates**
Loma Linda Transplantation Institute	**de Vera**
Dartmouth-Hitchcock Medical Center	**Dickson**
University of Texas Medical Branch	**Duchini**
Lourdes Medical Associates	**El-Genaidi**
Thomas Jefferson University	**Fenkel**
Albert Einstein Medical Center, Center for Liver Disease and Transplantation	**Feyssa**
Montefiore Medical Center	**Gaglio**
Kelsey Research Foundation	**Galler**
Orlando Infectious Disease	**Giron**
VA San Diego Healthcare System	**Ho**
Tampa General Hospital	**Neff**
Kaiser Permanente	**Nyberg**
Baystate Medical Center	**Paez**
Medical Procare, PLLC	**Pan**
Liver Wellness Center	**Williams**

INDUSTRY PARTNERS- KADMON, VERTEX, MERCK, GENENTECH

HCV-TARGET