May 2018: WHO Director General's Call to Action to Eliminate Cervical Cancer

World Health Organization

UN WOMEN

unicef

UNFPA UNAIDS

IAEA International Atomic Energy Agency

International Agency for Research on Cancer
World Health Organization

UNODC United Nations Office on Drugs and Crime

Unitaid

The Global Fund

Gavi

CLINTON HEALTH ACCESS INITIATIVE

uicc global cancer control
A MEMBERSHIP ORGANISATION FIGHTING CANCER TOGETHER

GHO Global Health Objectives

unfm Université Numérique Francophone Mondiale

NYU Langone Health

144th WHO Executive Board – 30 January 2019

More than 70 countries approved the decision for WHO secretariat to develop a

Global Strategy towards the Elimination of Cervical Cancer

Photo credit: Chris Black

Overview

1 HPV NAT Product overview

- Overview of existing and pipeline HPV nucleic acid testing (NAT) products
- HPV NAT programmatic considerations
- Review key features of NAT products

2 HPV Sample Collection Product overview

- Overview of sample collection products
- Highlights of key product features, and the role they can play within diagnostics networks

Approaches to Cervical Cancer Screening

3 approaches to Cervical Cancer Screening

Cervical Cancer Screening

Molecular

A. **Nucleic Acid tests (NAT)**
   - **HPV DNA**
     (e.g. Abbott, Roche Cobas, Qiagen, Cepheid Xpert, others)
   - **mRNA**
     (Hologic Aptima)

B. **Protein biomarkers**
   - **HPV antibodies**
   - **Oncoproteins**
     (e.g. OncoE6 / QIAsure)

Cytologic

A. **Conventional PAP smear**

B. **Liquid-based cytology (LBC)**

C. **Colposcopy+biopsy**

Visual Inspection

A. **Visual Inspection with Acetic Acid or with Lugol's Iodine (VIA / VILI)**

B. **Digital Imaging Approaches**
   - **i.e. Automated visual evaluation (AVE)**

NAT Testing Overview

- HPV NAT testing of oncogenic HPV types has been intensively studied over the past few years and proven to allow **earlier detection of persistent high-grade pre-cancer** compared to conventional cytology and VIA.
- Currently available tests detect **high-risk HPV infections** (hrHPV) including:
  - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
- NAT Platforms are classified as Conventional, Near-Point-of-Care, and Point-of-Care
  - Conventional platforms typically demonstrate higher throughput and lower pricing, however, require more advanced laboratory infrastructure and technician capacity while often reducing or delaying results return.

Advantages and Drawbacks of HPV NAT Testing

+ **Higher sensitivity allows longer interval between tests,** reducing the burden on the system and women

+ Reduction in cancer and related mortality is greater than using VIA due to increased sensitivity (WHO guidelines)

+ **Compatible with self-sampling,** which has been shown to be more acceptable and preferable to pelvic exam in several settings, enabling the possibility of increased screening coverage

---

– **High cost** compared to current cyotologic or visual-based methods

– **Low specificity for CIN2+** can lead to overtreatment

– Creates **increased demand on laboratory services** where personnel may be limited

– Current technologies often take several hours to analyse – **may be difficult with a single-visit screen** and treat procedure, which can be done with VIA

HPV NAT Commodities

4 types of commodities are required for HPV NAT

In order to run HPV NAT tests, **4 main types of commodities need to be procured** from suppliers.

	1	2	3	4
				
Products	**Proprietary Lab Items (Reagents and Consumables)**	**Non-Proprietary Lab Items**	**Sample Collection Device**	**Sample Collection Medium**
	Test Reagents + any controls/calibrators	Non-proprietary (generic) laboratory consumables such as: Gloves, pipette tips, lab gowns, etc. (50+ items used per test) **Non- specific to HPV NAT testing*	Device for collection of cervical or vaginal specimens through either self-collection or HCW collection Additional supplies (speculum, etc) required if HCW collection	Collection medium required to transport/store/prepare the sample
Suppliers	▪ Roche ▪ Abbott ▪ Hologic ▪ Cepheid ▪ BD ▪ Qiagen	▪ Roche ▪ Abbott ▪ LASEC	*Proprietary* ▪ Roche ▪ Abbott ▪ Hologic ▪ Qiagen *Non-Proprietary* ▪ Rovers ▪ Copan ▪ Aprovix AB	*Proprietary* ▪ Roche ▪ Abbott ▪ Qiagen ▪ etc *Non-Proprietary* ▪ SurePath ▪ Copan ▪ PreservCyt ▪ NSS

HPV NAT Commodities

4 types of commodities are required for HPV NAT

In order to run HPV NAT tests, **4 main types of commodities need to be procured** from suppliers.

	1	2	3	4
				
Products	**Proprietary Lab Items (Reagents and Consumables)**	**Non-Proprietary Lab Items**	**Sample Collection Device**	**Sample Collection Medium**
	Test Reagents + any controls/calibrators	lon-proprietary (generic) aboratory consumables uch as: loves, pipette tips, lab owns, etc. (50+ items used er test) *Non- specific to HPV NAT testing*	Device for collection of cervical or vaginal specimens through either self-collection or HCW collection Additional supplies (speculum, etc) required if HCW collection	Collection medium required to transport/store/prepare the sample
Suppliers	▪ Roche ▪ Abbott ▪ Hologic ▪ Cepheid ▪ BD ▪ Qiagen	▪ Roche ▪ Abbott ▪ LASEC	*Proprietary* ▪ Roche ▪ Abbott ▪ Hologic ▪ Qiagen *Non-Proprietary* ▪ Rovers ▪ Copan ▪ Aprovix AB	*Proprietary* ▪ Roche ▪ Abbott ▪ Qiagen ▪ etc *Non-Proprietary* ▪ SurePath ▪ Copan ▪ PreservCyt ▪ NSS

NAT Product Overview Key Features

NAT Products offer a menu of options that can be applied to a broad range of programmatic needs

			Program Considerations
Assay	Test Target	mRNA / DNA / signal amplification	Self sampling less accurate when using signal amplification-based test
	Genotype	All HR / HPV 16 & 18 Individual vs. aggregate	Individual identification can enable risk stratification (though not necessary)
	Performance	Sensitivity/specificity for CIN2+ lesions	Low sensitivity – missed opportunities Low specificity – overtreatment
Workflow / Platform	Throughput	Number of tests in 8 hours	Allows for testing of higher patient volumes
	Same-day	Ability to produce same-day results	Same day testing preferable for populations with high risk for LTFU
	Random Access	Batching vs. Random Access	Random access preferable in settings with varied or unpredictable volumes
	Multiplexing capabilities	Platform testing capacity beyond HPV	Ability to leverage existing infrastructure
Other	Costs	Assay and Platform specific costs	Affordability

NAT Product Pipeline Overview

12+ Screening tests are available on the market, with 4+ in the pipeline

Commercially available

In the pipeline

	HPV NAT
Advanced Lab	Cobas HPV – 4800/6800/8800 - Roche
	RealTime High Risk (HR) HPV – m2000 sp/rt – Abbott
	Aptima HPV – Panther - Hologic
	Cervista HPV 16/18 – Cervista HTA – Hologic
	Alinity m High Risk (HR) HPV – Alinity m - Abbott
	Digene HC2 High Risk HPV – Rapid Capture System – Qiagen
	Onclarity HPV Assay – Viper LT – BD
Near POC	*care*HPV – *care*HPV Test System – Qiagen
	Xpert HPV – GeneXpert IV – XVI – Cepheid **
	Venus HPV – Autrax + Life 96 PCR – LifeRiver Biotech
	Harmonia HPV – Autrax + Life 96 PCR – LifeRiver Biotech
	Ampfire HPV – rtPCR – Atila Biosystems
	PreTect SEE – non-proprietary thermal cycler – PreTect
	Truenat HPV-HR – Truelab PCR – Molbio *
Point of Care	Q-QAS HPV – Q-POC – QuantumDx
	NEDxA – *TBC* – Genomica

**Currently available in India, though not yet available globally*

***Cepheid Omni and Edge HPV products in pipeline*

Role of Conventional HPV NAT Tests

Advantages

- Ability to leverage substantial **existing testing capacity**
- Efficiencies across established laboratory systems
  - Data management, sample transportation, human resources, service & maintenance agreements, etc already in place
- **High throughput testing** allows for screening of large numbers of patients

Limitations

- Delayed return of results (long TAT) with potential for loss-to-follow-up
- In-ability to establish **same-day test and treat**

Relevant Conventional Products on Market

Deep Dive into **3** conventional instruments offering HPV NAT

Assay	*Real*Time High Risk (HR) HPV	cobas® 4/6/8800 HPV	Aptima HPV
Platform	**m2000 sp/rt**	**4/6/8800**	**Panther**
Manufacturer/ Developer	**Abbott**	**Roche**	**Hologic**
Test Target	HPV **DNA** (L1 gene) Target Amplification	HPV **DNA** (L1 gene) Target Amplification	E6, E7 **mRNA** Target (Isothermal) Amplification
Genotypes	HPV 16, 18, **(individually)** 12 other HR: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	HPV 16, 18 **(individually)** 12 other HR: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 **(cannot distinguish individual types)**
Regulatory Approval	CE	FDA* / CE	FDA / CE
Performance (sensitivity & specificity for CIN2+)	Sens: 96.4% Spec: 92.0% *(Carozzi, 2011)*	Sens: 90%/98.3% Spec. 94.6%/86.2% *(Heideman,2011/Lloveras, 2013)*	Sens: 55.3-100% Spec: 77-96.3% *(Haedicke 2016)*
8 Hour Throughput	96	192 (4800), 384 (6800), 1,056 (8800)	96
Random Access	Batched	Batch (4800) Random Access (6/8800)	Random Access
Same-Day Screening	X	X	X
Platform Multiplexing Capabilities (not exhaustive	HIV-1 Qual, HIV-1 Quant, HPV, HBV, HCV, MTB, CT, CT/NG, MTB/RIF, CMV, EBV,	HIV-1 Qual, HIV-1 Quant (4800), HBV, HCV, HSV-1/2, CT/NG, MTB/RIF, MRSA/SA	HIV-1 Qual, HIV-1 Quant, HPV, HBV, HCV, HSV-1/2, CT/NG, TV, Zika
Per Test Pricing	$10.50 (**all-inclusive;** no sample collection)	$8.90** (CPT & incl. controls, no sample collection)	$12.00 (**all-inclusive;** incl. sample collection)

**Only cobas 4800 is FDA approved*

***estimated all-in (incl. sample collection = $17.29 - $19.33)*

Additional Conventional Products on Market

Assay	Onclarity HPV Assay	Digene Hybrid Capture 2 High-Risk HPV DNA test
Platform	Viper LT	Modular system & Rapid Capture System-RCS
Manufacturer/ Developer	BD	Qiagen
Test Target	HPV **DNA** (E6/E7) Target Amplification	HPV **DNA** Test Signal Amplification
Genotypes	HPV types 16, 18, 31, 45, 51, 52 (**individually**) 8 other genotypes in three groups (33/58, 56/59/66, 35/39/68)	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 **(cannot distinguish individual types)**
Regulatory Approval	FDA / CE	FDA / CE
Performance (sensitivity & specificity for CIN2+)	Sens: 97% Spec: 90% *(Ejegod, 2016)*	Sens: 94.6% Spec: 94.1% *(Mayrand, 2007)*
8 Hour Throughput	192	384 (6800) / 1,056 (8800)
Random Access	Batched	Batched
Same-Day Screening	X	X
Platform Multiplexing Capabilities (not exhaustive	ProbeTec QX GC, ProbeTec QX CT	TBC
Per Test Pricing (ex-works)	TBC	$11.00 (estimate)
Device Cost	TBC	TBC

**Additional marketed products include Harmonia and Venus HPV tests from LifeRiver Biotech; QIAscreen HPV from Qiagen, and Cervita HPV from Hologic*

Role of Near-POC HPV NAT Tests

Advantages

- Improved opportunity for decreased turnaround time which may decrease LTFU
  - Potential for same-day testing
- Amenable to decentralization of testing
- Ability to leverage substantial **existing testing capacity and network** (Cepheid)

Limitations

- Higher cost than conventional testing limits accessibility
- Lower throughput devices and near-POC placement could limit same-day testing
- Increases complexity of fleet management (QA, S&M, supply chain)

Near POC Products on Market

Deep Dive into **4** Near POC instruments offering HPV NAT

Assay	careHPV	Xpert® HPV
Platform	careHPV Test System	GeneXpert (IV, XVI)*
Manufacturer/ Developer	Qiagen	Cepheid
Test Target	HPV DNA Signal Amplification	HPV DNA (E6/E7) Target Amplification
Genotypes	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 **(cannot distinguish individual types)**	HPV 16, 18/45 **(individually)** 11 other hrHPV: 31, 33, 35, 39, 51, 52, 56, 58, 59, 66, 68
Regulatory Approval	CE / WHO PQ	CE / WHO PQ
Performance (sensitivity & specificity for CIN2+)	sens: 88% spec 84% (Kelly H, 2017)	Sens 94% Spec: 83% (Cuschieri, 2016)
8 Hour Throughput	Up to 270	32 - 128
Random Access	Batch	Random access
Same-Day Screening	X *(2.5 hrs to first result)*	✓ *(60 min to first result)*
Platform Multiplexing Capabilities (not exhaustive)	None	HIV-Qual, HIV-Quant, HPV, HBV-VL, HCV-VL, MTB, MTB-RIF, CT, TV, MG, GC, Flu, Flu/RSV, EV, C. diff, MRSA
Per Test Pricing (*ex-works*)	$5.00	$14.90**
Device Cost	$10,500	$17,000

**Other GeneXpert models include Infinity-48 and Infinity-80. To be available soon on GeneXpert Edge.*

***Estimated all-in pricing (incl. sample collection) = $27.80*

Near POC Products on Market

Deep Dive into **4** Near POC instruments offering HPV NAT

Assay	Ampfire HPV (Geotype 15 hr HPV)	Truenat HPV-HR
Platform	**rt PCR** *(proprietary POWERGENE 9600 PLUS)*	**Truelab PCR analyzer**
Manufacturer/ Developer	**Atila Biosystems**	**Molbio**
Test Target	HPV DNA Target (isothermal) amplification	HPV DNA
Genotypes	HPV16/18 **(individually)** 13 other hrHPV: 31, 33, 35, 39, 45, 51, 52, 53, 56, 59, 66, 68, 82	16/31 and 18/45 types
Regulatory Approval	CE-IVD	TBD
Performance (sensitivity & specificity for CIN2+)	No peer-reviewed data for clinical sensitivity or specificity	TBD
8 Hour Throughput	up to 672 in 8 hr period 96 samples per run	TBC
Random Access	Batch	Batch
Same-Day Screening	✓ *(90 min to first result)*	TBC
Platform Multiplexing Capabilities (not exhaustive)	Below kits only for research use: HSV, Strep, c diff, pneum, salm, staph, strep, NIPT	TB, HCV, HIV, malaria, etc
Per Test Pricing (ex-works)	$4.50	$14.50 - $17.30
Device Cost	$16,000	<$5,000 (TBC)

Role of POC HPV NAT Tests

Advantages

- Significant improvements to test turn-around-time
  - Allows for same-day test–and–treat with minimal loss-to-follow-up particularly in patients that are hard to track
- Enables access to remote sites or with limited infrastructure

Limitations

- Low throughput devices may generate backlog if not placed efficiently
- Not currently available and potential AVE redundancy if market entry is delayed
- Additional burden on health care providers
- Increases complexity of fleet management (QA, S&M, supply chain)

Promising POC NAT Product in Pipeline

Deep Dive into **1** pipeline NAT assays

Assay	Q-CAS HPV
Platform	Q-POC
Manufacturer/ Developer	QuantuMDx/ Global Good
Test Target	HPV DNA Target amplification
Genotypes	14 hrHPV (**individually)**
Regulatory Approval	
Performance (sensitivity & specificity for CIN2+)	
8 Hour Throughput	TBC
Random Access	Random Access
Same-Day Screening	✓ *(Time to first result TBC)*
Platform Multiplexing Capabilities (not exhaustive	TBC
Per Test Pricing (ex-works)	TBC
Device Cost	TBC

Additional Biomarker and Oncoprotein tests
Currently marketed products

Oncoproteins (E6 and E7)

- Necessary and a key step in the progression to cancer
- Occurs only after integration, so would not be positive in transient superficial infection only
- Experimental and performance characteristics have not been entirely worked out
- Not currently included in guidelines
- Ideal collection and testing conditions have not been established

Company	Test name	Biomarker	Genotypes	Sensitivity/ Specificity	Throughput /Batching	Regulatory	Format
Arbor Vita	OncoE6	E6 protein	16,18	Sens: Low Spec: Medium	96 in 8hrs Batched	CE-IVD	Lateral Flow
InCellDx	OncoTect	E6/E7 mRNA	16,18	TBD	TBD	CE-IVD	Flow Cytometry

NAT Testing – Key Takeaways

- HPV NAT provides an opportunity to implement a **more sensitive** test than current visual-based methods for detection of cervical precancer
- With lower specificity for CIN2+, programs need to be mindful of **potential for overtreatment** and carefully consider their testing algorithms (i.e. test-triage-treat vs. test-treat)

- HPV NAT provides as unique opportunity for self-sampling alleviating HCW burden, improving screening acceptability and therefore may increase screening coverage
- Current testing options are **predominantly lab-based**, which limits the opportunity for screen and treat

- Costs remain high (>$10 per test all-in), which may limit shift from visual examination to enable testing scale-up to both low-risk and high-risk women
- Synergies can be generated by leveraging multiplexing capabilities of diagnostic devices