## NATIONAL CANCER GRID (NCG) OF INDIA TATA MEMORIAL CENTER

# Consensus Evidence Based Resource Stratified Guidelines on Secondary prevention of Cervical, Breast & Oral Cancers

## NCG WORKING GROUP

Resource Stratified guidelines for Preventive Oncology and Primary Care.

## **SUMMARY**

## **RESOURCE-STRATIFIED CLINICAL PRACTICE GUIDELINE SUMMARY**

The National Cancer Grid (NCG) formed in 2012 funded by the Government of India through the Department of Atomic Energy, is amongst the largest cancer networks in the world formed with the primary mandate of working towards uniform standards of patient care across India by adopting evidence-based cancer prevention, screening and management guidelines, which are implementable across the country.

## **RATIONAL FOR DEVELOPMENT OF RESOURCE STRATIFIED GUIDELINES**

WHO Guidelines for screening of Oral, Breast and Cervical cancers for LMIC settings are currently available. However, there are challenges for their adoption and implementation due to large disparities and variations in the availability and access to health care resources. Recently Government of India have also released broad programmatic guidelines, mainly focused on opportunistic screening within the existing public health systems framework. These pose unique challenges such as cost of administration, training of manpower, access to screening facilities, follow up management and adequate linkages for confirmatory diagnosis and subsequent treatment. The development of public health care systems varies across different States in the country as health is a State subject. The health resources allocated towards cancer control also vary between different States in the country. Hence evidence based screening, diagnosis and management protocols for common cancers need to be developed to suit different levels of health resource settings. This will enable identifying the most suitable options for adaptation to the local context.

Considering the complexities involved in delivering population based cancer screening programs and the diversity of health system capabilities with in different regions in India, the National Cancer Grid (NCG), a consortium of more than 180 cancer institutions in India, the largest cancer networks in the world, aims to provide evidence based resource stratified strategies and approaches that are operationally feasible to help adopt best practices in a wide range of situations stratified by resources, leveraging with existing health system.

The NCG consensus guidelines and algorithms are consistent with existing evidence and appropriate in the context of health systems of our country, for a sustainable implementation of population based cancer screening and early detection program.

## TABLE 1: Summary of the Resource-Stratified Clinical Practice Guideline for SecondaryPrevention of Cervical Cancer: NCG INDIA

		ESSENTIAL/ LIMITED RESOURCE	OPTIMAL/ ENHANCED RESOURCE	OPTIONAL / HIGH RESOURCE
1	Primary Screening methods	Visual inspection with acetic acid (VIA)	Human papillomavirus (HPV) DNA	Human papillomavirus (HPV) DNA
2	Where : Place for screening	Health & Wellness Centers Primary Health Centers (PHC), Community Health Centers (CHC)	Health & Wellness Centers Primary Health Centers (PHC), Community Health Centers (CHC)	District Hospitals (DH) Private Health Care Facilities
3	By Whom	Trained Primary Care Workers Trained Nurse	Trained Nurse Physician	Trained Nurse Physician
4	Target screening ages	30-65 years	30-65 years	25-65 years
5	Frequency of screening	One to three times in a lifetime	10 years if two consecutive negative tests at 5- year intervals,	5 years
6	Exiting Screening	Resource dependent	65 years of age or older with consistently negative results over the past 15 years.	65 years of age or older with consistently negative results over the past 15 years.
7	Use of triage and Diagnostic steps	VIA : See and Treat	Cytology (Quality Assured) VIA	HPV 16/18 Genotyping Cytology: Quality Assured
8	After Triage		NEGATIVE: Follow-up in 12 months ABNORMAL /POSITIVE: Colposcopy if available	NEGATIVE: Follow-up in 12 months ABNORMAL /POSITIVE: Colposcopy / directed Biopsy

PageJ

			Visual assessment for treatment (VAT) if colposcopy is not available.	
9	Opportunity for implementing screen-and- treat approaches	Yes	Resource dependent	NOT Recommended
10	Treatment of Women With Precursor Lesions	Cryotherapy: Lesions suitable for cryotherapy Loop electrosurgical excision procedure (LEEP): Lesions not suitable for cryotherapy	Loop electrosurgical excision procedure (LEEP).	Loop electrosurgical excision procedure (LEEP).
11	Post- treatment follow-up	One month & Twelve-month post-treatment follow-up is recommended for all settings		
12	Special Populations: Women who are HIV positive or immunosuppr essed for other reasons	primary screening 6 weeks postpartum		

## TABLE 2 : Summary of the Resource-Stratified Clinical Practice Guideline for SecondaryPrevention of Breast Cancer: NCG INDIA

		ESSENTIAL/ LIMITED RESOURCE	OPTIMAL/ ENHANCED RESOURCE	OPTIONAL / HIGH RESOURCE
1	Primary Screening methods	Clinical Breast Examination (CBE)	Clinical Breast Examination (CBE)	Clinical Breast Examination (CBE) + Conventional digital Mammography
2	Where : Place for screening	Health & Wellness Centers Primary Health Centers (PHC),	Health & Wellness Centers Primary Health Centers (PHC),	Health & Wellness Centers (if Mammography facilities are available)
		Community Health Centers (CHC)	Community Health Centers (CHC)	Community Health Centers (CHC) (if Mammography facilities are available) District Hospitals (DH) Tertiary Health care settings Private Health Care
3	By Whom	Trained Primary Care Workers Trained Nurse	Trained Nurse Physician	Trained Nurse Physician / Breast Surgeon
4	Target screening ages	40-65 years	40-65 years	Women aged 40-49 : CBE + Mammography depending on Risk assessment and advise of the Physician Women aged >50 -75: CBE + Conventional Mammography
5	Frequency of screening	One to three times in a lifetime	2 years	2 years

6	Exiting Screening	75 years	75 years of age or older	75 years of age or older
7	Diagnostic steps	IMAGING 1. Mammography 2. Ultrasonography TISSUE DIAGNOSIS CYTOLOGY/PATHO LOGY 3. FNAC 4. Core biopsy	<ol> <li>Mammography</li> <li>Ultrasonography</li> <li>Core biopsy         <ul> <li>As appropriate (as per availability</li> <li>of infrastructure and facilities)</li> </ul> </li> </ol>	Core biopsy
8	Treatment of Women	Refer to Tertiary Centre. Management of treatment as per standard guidelines.	Refer to Tertiary Centre. Management of treatment as per standard guidelines.	Refer to Tertiary Centre. Management of treatment as per standard guidelines.

 TABLE 2 : Summary of the Resource-Stratified Clinical Practice Guideline for Secondary

 Prevention of Oral Cancer: NCG INDIA

		ESSENTIAL/ LIMITED RESOURCE	OPTIMAL/ ENHANCED RESOURCE	OPTIONAL / HIGH RESOURCE
1	Primary Screening methods	Oral Visual Inspection (OVI)	Oral Visual Inspection (OVI	Oral Visual Inspection (OVI
2	Where : Place for screening	Health & Wellness Centers Primary Health Centers (PHC), Community Health Centers (CHC)	Health & Wellness Centers Primary Health Centers (PHC), Community Health Centers (CHC)	District Hospitals (DH) Secondary / Tertiary Health care settings Private Health Care Eacilities
3	By Whom	Trained Primary Care Workers Trained Nurse	Trained Nurse Dentists, General practitioners	Physician/Surgeons/ Dentist
4	Target Group	At Risk population: Use of Tobacco / Alcohol / Areca nut / Mixed use	At Risk population: Use of Tobacco / Alcohol / Areca nut / Mixed use	At Risk population: Use of Tobacco / Alcohol / Areca nut / Mixed use
5	Target screening ages	All age groups 15 years and older	All age groups 15 years and older	All age groups
6	Frequency of screening	One to three times in a lifetime	5-year intervals	2 years
7	Counselling on tobacco cessation	Tobacco cessation Counselling by Trained Primary Care Workers	Tobacco cessation Counselling by Trained Medical Social Workers	Tobacco cessation Counselling by Trained Medical Social Workers/ Physician
8	Triage steps	OVI Positive Evaluation by Doctor at PHC/CHC/DH (including Dentist)	OVI Positive Evaluation Primary care dental and General practitioners	OVI Positive Evaluation by General Surgeon/ ENT Surgeon including Dentist

Page

			Evaluation by General Surgeon/ ENT Surgeon including Dentist at DH.	
9	Diagnostic Confirmation	NEGATIVE: Follow-up in 12 months ABNORMAL /POSITIVE: Diagnosis by Oral punch at PHC Excision Biopsy at CHC /DH	NEGATIVE: Follow-up in 12 months ABNORMAL /POSITIVE: Diagnosis by Oral punch / Excision Biopsy at CHC /DH	NEGATIVE: Follow-up in 12 months ABNORMAL /POSITIVE: Diagnosis by Oral punch / Excision Biopsy at Tertiary center
10	Treatment of Precursor Lesions	Surgical Excision at DH	Surgical Excision at DH	Surgical Excision / Laser Excision at Tertiary center
11	Post-treatment follow-up	Twelve-month post-treatment follow-up is recommended for all settings		

## **CERVICAL CANCER SCREENING:**

## CERVICAL CANCER INCIDENCE AND MORTALITY:

Cervical cancer is the fourth most common cancer affecting women worldwide, after breast, colorectal, and lung cancers, with 570,000 cases and the fourth leading cause of cancer death in women with 311,000 deaths in 2018 worldwide. India accounted for 25% of global cervical cancer mortality burden in 2018. (GLOBOCAN) Cervical cancer incidence rates varied across population based cancer registries (PBCR) in India with a mean Age Standardised Rate (ASR) of 22.0 per 100,000.

Considering the evidence generated till date for cervix cancer screening modalities for early detection of cervical cancers, we present in this document, the current evidence based recommendations that can be adopted for India for implementing cervical cancer screening and pre cancer management strategies that will help address the gaps in uniform implementation at different resource settings in India.

## I. CHOICE OF THE SCREENING TEST: OPTIMAL RESOURCE SETTING

## a. High Risk HPV (hrHPV) testing in primary screening

In the past 20 years, large cross sectional studies designed to evaluate the performance of high-risk human papillomavirus (hrHPV) testing have demonstrated the sensitivity of hrHPV testing at 66–95%, with specificity between 76% and 95%. HPV test is the most sensitive among all the screening tests available till date. A large randomized study in India demonstrated that even a single round of HPV test followed by appropriate management of the screen positive women could reduce the cervical cancer mortality by 50%. The other advantages of the test are – the test is objective and highly reproducible, training needs are not very stringent, point of care tests are now available. The high negative predictive value of the test can allow prolongation of screening interval up to 10 years in the screen negative women.

**RECOMMENDATIONS:** HPV DNA testing as primary screening test has been adopted in many national programs globally in High and Middle Income resource settings. HPV testing can replace cytology as a primary screening tool in setups which can afford HPV Screening.

In women who test negative on an HPV test, rescreening should be done after a minimum interval of five years.

## b. Conventional Cytology:

Organised cytology-based cervical screening in the Europe, North America and Australia led to a substantial reduction of the incidence of cervical cancer in these regions in the past five decades. Successes of the cytology based screening programs were mainly due to repeated testing at frequent intervals, high population coverage, and quality-control procedures adopted in these regions.

The test has several limitations particularly for resource constrained settings – need for highly skilled cytotechnicians and pathologists, high infrastructural requirements, need for stringent quality control at each step.

**RECOMMENDATIONS:** Can be recommended in Opportunistic Health settings with Quality Assured program.

## c. Co testing

Co-testing is no longer recommended for cervical cancer screening.(European QA guidelines)

**RECOMMENDATIONS:** If resources permit, HPV testing should be the test of first choice.

#### II. CHOICE OF THE SCREENING METHOD: RESOURCE CONSTRAINED SETTING

## **1.** Appropriate screening technologies for LMIC:

## a. Visual Inspection with Acetic Acid (VIA)

Visual inspection with acetic acid (VIA) is simple, non invasive and inexpensive visual test, has easy to learn approach, does not require laboratory involvement, is a real time test with results available immediately and even non-physicians can be trained to perform the procedure. The efficiency and cost-effectiveness of Visual inspection with acetic acid (VIA) has been evaluated in two Randomized Control Trials (RCT) showing a significant mortality benefit following VIA cervical screening. [35% South India ,31% Mumbai]. The advantages of VIA are higher sensitivity than cytology, immediate availability of results allowing management decisions to be taken at the same visit, feasibility of the test being performed by trained nurses of health workers and low cost. More recently, Sauvaget and colleagues, after pooling 26 studies from low- and middle income provided summary estimate of VIA accuracy for sensitivity of 80% (range, 79%–82%), specificity of 92% (range, 91%–92%), PPV of 10% (range, 9%–10%), and NPV of 99%. Effects of factors such as region, capacity of screener (health worker, nurse, or physician), place of screening, study period, and size of study population had no effects on VIA accuracy demonstrating the overall reliability of VIA screening

**RECOMMENDATIONS:** Visual inspection using acetic acid (VIA) can be adopted as the screening modality of choice in settings where resources are not adequate to provide HPV testing.

## 2. Appropriate Age For Screening & Screening Frequency.

**RECOMMENDATIONS:** Twice in a life time Screening between Age of 30 and 49 can be highly protective and cost-effective which can be considered in Indian context where screening coverage is extremely low.

#### **III. MANAGEMENT & TREATMENT FOR PRE-INVASIVE DISEASE**

A screening program will be effective only when there is a mechanism to ensure high compliance of the screen positive women for further diagnosis and treatment.

#### **3 A.** Treatment for Pre-Invasive disease

#### **RECOMMENDATIONS:**

**1.** For all screen-and-treat recommendations, cryotherapy or thermo-coagulation is the first-choice treatment for women who have screened positive and are eligible for ablative treatment.

2. Cryotherapy or thermo-coagulation can be safely administred at the primary care facility if staff are appropriately trained .

3. When women have been assessed as not eligible for ablative therapy, LEEP is the alternative treatment or cold knife conization (CKC).

4. Hysterectomy is not the treatment for CIN and should only be reserved for the women with recurrent lesion in whom fertility preservation is not required. Even in these women invasive cancer should be carefully ruled out after colposcopy directed biopsies or LEEP.

#### **3** B. Adopting Single visit and See- Treat approaches.

WHO has recommended VIA based Screen and Treat programs for better compliance to cervical pre cancer treatment especially in regions with poor access to health care facilities.

**RECOMMENDATIONS:** Primary screening by VIA gives immediate results, which when linked to cryotherapy facilities to permit a single-visit Screen & Treat strategy. [Algorithm for Primary Screening by VIA. CHART 1]

## IV. SCREENING AND DIAGNOSIS : WHERE AND BY WHOM?

## **RECOMMENDATIONS:**

- **1.** Para Medical workers like ANMs can be trained to perform VIA at Subcentre level and above.
- Screen positives should be evaluated for confirmation of the diagnosis at Primary Health Centers (PHC), Community Health Centers (CHC) and District Hospitals (DH) by available modalities like cytology, Colposcopy guided biopsy.
- **3.** Biopsies to be performed at PHC, CHC and DH.
- 4. See and treat approach can be practiced at PHC and above levels.
- 5. Colposcopy, biopsy and treatment of precancerous lesion at District hospitals.

## CHART 1 : Cervical Cancer Screening \_Primary Screening by VIA & management

## of VIA positive Women



CHART 2: Cervical Cancer Screening \_Primary Screening by HPV DNA Test & Management of women after a positive HPV primary screening test.



## CHART 3: Cervical Cancer Screening \_ Abnormal Pap Cytology Investigation and Follow Up



Page 16

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Page 17

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#### **BREAST CANCER SCREENING**

Breast cancer is the most common cancer and most common cause of cancer related death among women globally and also in India. An estimated 208,8849 new breast cancer cases were diagnosed globally in 2018, accounting for 24.2% of all female cancers and the fourth leading cause of death due to cancers in females with nearly 626,679 women deaths due to breast cancer. In India the Age Standardised Incidence rate for breast cancer was reported at 24.7 per 100,000 with 162,468 new cases.

#### Methods of Screening for Breast Cancer:

Mammography is the most widely used screening modality, with evidence of benefit for women aged 40 to 74 years. Clinical breast examination and breast self-exam have also been evaluated but are of uncertain benefit. Technologies such as ultrasound, magnetic resonance imaging, tomosynthesis, and molecular breast imaging are being evaluated, usually as adjuncts to mammography.

#### Mammography:

Mammography screening has been shown to be associated with a reduction in breast cancer mortality across a range of study designs, including RCTs and observational studies (trend analyses, cohort studies, and case-control studies), with most studies demonstrating a significant benefit. Evidence suggests that mammography screening performed every 12 to 33 months is effective in decreasing breast cancer mortality. Large proportion of the benefit of screening mammography is maintained by biennial screening.

Screening for breast cancer is associated with false-positive findings leading to recall for additional imaging or biopsy in women without cancer. The estimates of over diagnosis vary widely, from less than 5% to more than 50%.

A mammography screening program is complex multidisciplinary undertaking. Accuracy of screening mammography is dependent on factors related to requirement of high-quality instrumentation and trained radiologists and involves substantial resources and *National Cancer Grid: Resource Stratified Guidelines\_2019/Preventive Oncology* 

infrastructure, which are not within the reach of most LMICs and hence mammography screening is considered not cost-effective for a lower-middle income country.

#### **Clinical Breast Examination (CBE):**

The Canadian National Breast Screening Study- 2, that compared CBE with CBE + Mammography, did not show any added benefit of adding mammography to CBE. (1,2) The intermediate analysis of the Trivandrum RCT initiated in 2006 showed early stage detection of breast cancers with CBE. (3) The Mumbai RCT with CBE, which is one of the largest and oldest trial with biennial CBE offered four times in one arm versus no screening in the other arm has shown downstaging with CBE for all age groups (4) and breast cancer mortality reduction among women more than 50 years. (personal communication, in process of publishing)

CBE screening in India may be valuable, practical and cost effective option in LMICs. Training health workers in CBE and using these trained personnel to implement early detection programmes for breast cancer may provide the only opportunity for women in LMICs to undergo regular breast examination for early detection of breast cancer.

#### **Breast Self-Examination**

Breast self-examination (BSE) has been compared with usual care (no screening activity) and has not been shown to reduce breast cancer mortality.

#### Ultrasonography

The primary role of ultrasound is in the diagnostic evaluation of palpable or mammographically identified masses, rather than a primary screening modality. A consensus statement by the European Group for Breast Cancer Screening on screening of breast cancer using ultrasound examination concluded that ultrasound is an important adjunct to mammography and clinical examination in the further assessment of both palpable and impalpable breast abnormalities.

#### **RECOMMENDATIONS: OPTIMAL-RESOURCED SETTINGS**

## A. Women Aged 50–69 Years: Asymptomatic and at Average Risk For Breast Cancer

WHO recommends organized, population based mammography screening programmes for women aged 50–69 years if the conditions for implementing an organized programme specified are complied by the health-care system. Screening interval of two years.

## B. Women Aged 40–49 Years: Asymptomatic and at Average Risk For Breast Cancer

WHO suggests an organized, population-based screening programme for women aged 40–49 years only if such programme is conducted in the context of rigorous research and monitoring and evaluation

## C. Women Aged 70–75 Years: Asymptomatic and at Average Risk For Breast Cancer

WHO suggests Conditional recommendation based on low quality evidence

## **RECOMMENDATIONS: LIMITED RESOURCE SETTINGS:**

## A. Women Aged 50–69 Years: Asymptomatic and at Average Risk For Breast Cancer

Clinical Breast Examination, a low-cost screening method, seems to be a promising approach for these settings and could be implemented when the necessary evidence from ongoing studies becomes available.

#### B. Women Aged 40–49 Years: Asymptomatic and at Average Risk For Breast Cancer

Clinical Breast Examination in population-based screening programmes for women aged 40–49 years.

## C. Women Aged 70–75 Years: Asymptomatic and at Average Risk For Breast Cancer

WHO recommends against the implementation of population-based screening programmes

## **BREAST HEALTH / BREAST AWARENESS:**

Need to address the value of increasing breast awareness and in improving accessibility for early clinical diagnosis and prompt treatment in health services









#### CHART 1: Breast Cancer Screening \_Medium to High Resource Settings

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#### **ORAL CANCER SCREENING**

Oral cancer is an important public health problem with increasing incidence and late-stage presentation. Cancers of the mouth , pharynx and larynx taken together are the seventh most commonly occurring type of cancer worldwide. India reported Lip, oral cavity cancer at ASIR of 9.1 for both sexes combine and 13.9 for men. Oral cancer thus accounts as the highest incidence of malignancy in males and the second highest in females in India.

Smoking, alcohol use, smokeless tobacco use, and HPV infection are the major risk factors for oral cavity cancer. Smokeless tobacco products and betel quid with or without tobacco are the major risk factors for oral cavity cancer in India and other neighbouring countries. Human papillomavirus (HPV) has been shown to be another independent risk factor for oral squamous cell carcinomas (OSCC) of the base of the tongue, tonsils, pharynx, and larynx.

Despite the general accessibility of the oral cavity during physical examination, many malignancies are not diagnosed until late stages of disease. Early detection of oral cancer and their precursors is the key to reducing the high mortality rate attributable to oral cancer.

#### **Oral Cancer screening**

The screening tests or diagnostic aids used to improve early detection and diagnosis of oral precancers and cancers which are available for oral cancer, some of which have been practiced and studied for many years while others have recently become commercially available include Oral Visual examination, exfoliative cytology, vital tissue staining (toluidine blue, Methylene blue), visualization adjuncts (ViziLite Plus with TBlue, ViziLite, Microlux DL, Orascoptic DK, VELscope), and OralCDx brush biopsy.

#### **Oral Visual Inspection (OVI)**

A conventional oral visual inspection (OVI) of the oral cavity, using normal (incandescent) light, has long been the standard method for oral cancer screening. The UK working group on

screening for oral cancer and precancer in 1990's had concluded that the most suitable screening for oral cancer and precancer is a thorough and methodical examination in good lighting of the mucosal surfaces of the oral cavity. A meta-analysis of four studies of OVI conducted in developing countries using health care auxiliaries as screeners showed an overall sensitivity of 0.85 (95% CI 0.73, 0.92) and specificity of 0.97 (95% CI 0.93, 0.98) indicating a satisfactory test performance for an oral examination.

Results of community-based cluster randomized controlled intervention trial in Trivandrum district, Kerala, South India, showed significant 34% reduction in oral cancer mortality among users of tobacco or alcohol, or both and a much higher reduction in those complying with all rounds of screening in a randomized trial in India. Although OVI could be considered as an effective as a screening test, there are still many problems with this approach since , the vast majority of the precancer lesions detected are benign and only a small percentage of leukoplakias are progressive or become malignant thus OVI cannot discriminate between potentially premalignant lesions and non-progressive lesions.

#### Mouth Self Examination (MSE)

As an alternative Mouth Self Examination (MSE) was evaluated in a study involving 34,766 subjects in India and was found to have low sensitivity of 18% while the specificity was 99.9%. Overall awareness about oral cancer and its risk factors after introduction of MSE program was over 80%; but the compliance to seek treatment was reported to be very poor at 32%. The authors concluded that role of health education in sustained practice of MSE needs to be evaluated.

**Adjunctive Technologies:** There is currently no evidence to support the use of like , vital tissue staining (toluidine blue, Methylene blue), visualization adjuncts (ViziLite Plus with TBlue, ViziLite, Microlux DL, Orascoptic DK, VELscope), as a screening tool to reduce oral cancer mortality.

#### CONCLUSION

There has been a dramatic increase in the development of tools and devices for oral cancer screening in the last few decades. However no technology to date has provided definitive evidence to suggest that it improves the sensitivity or specificity of oral cancer screening beyond OVI alone. Most studies conducted for these newer devices have been performed in a setting used to aid in the diagnosis of a lesion that has already been identified by the naked eye, rather than as true screening tools.

Effective early detection technologies that are easy to perform clinically in primary care settings combined with an increased public awareness of oral cancer in general will help attain the goal of decreasing the burden of oral cancer.

### **DIAGNOSTIC EVALUATION**

**Oral Brush Cytology:** Standard exfoliative oral cytology from the mucosal surface and has been existence for a long time but has proven unreliable so far.

**Oral Brush Biopsy:** Brush Biopsy was designed for evaluating clinical lesions that would not be subjected to standard biopsy due to lack of facilities. Several studies have shown encouraging results with oral brush cytology for evaluation of oral precancerous lesions. This may have application in resource challenged areas and could be a risk free method of evaluating oral lesions.

#### **CHART : Oral Cancer Screening**



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