

**GLOBAL LEADERS IN
GENOMIC MEDICINE MEETING**

Indian Perspective



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Advisor**

**Department of Biotechnology
Ministry of Science and Technology**

STRUCTURE OF THE PRESENTATION

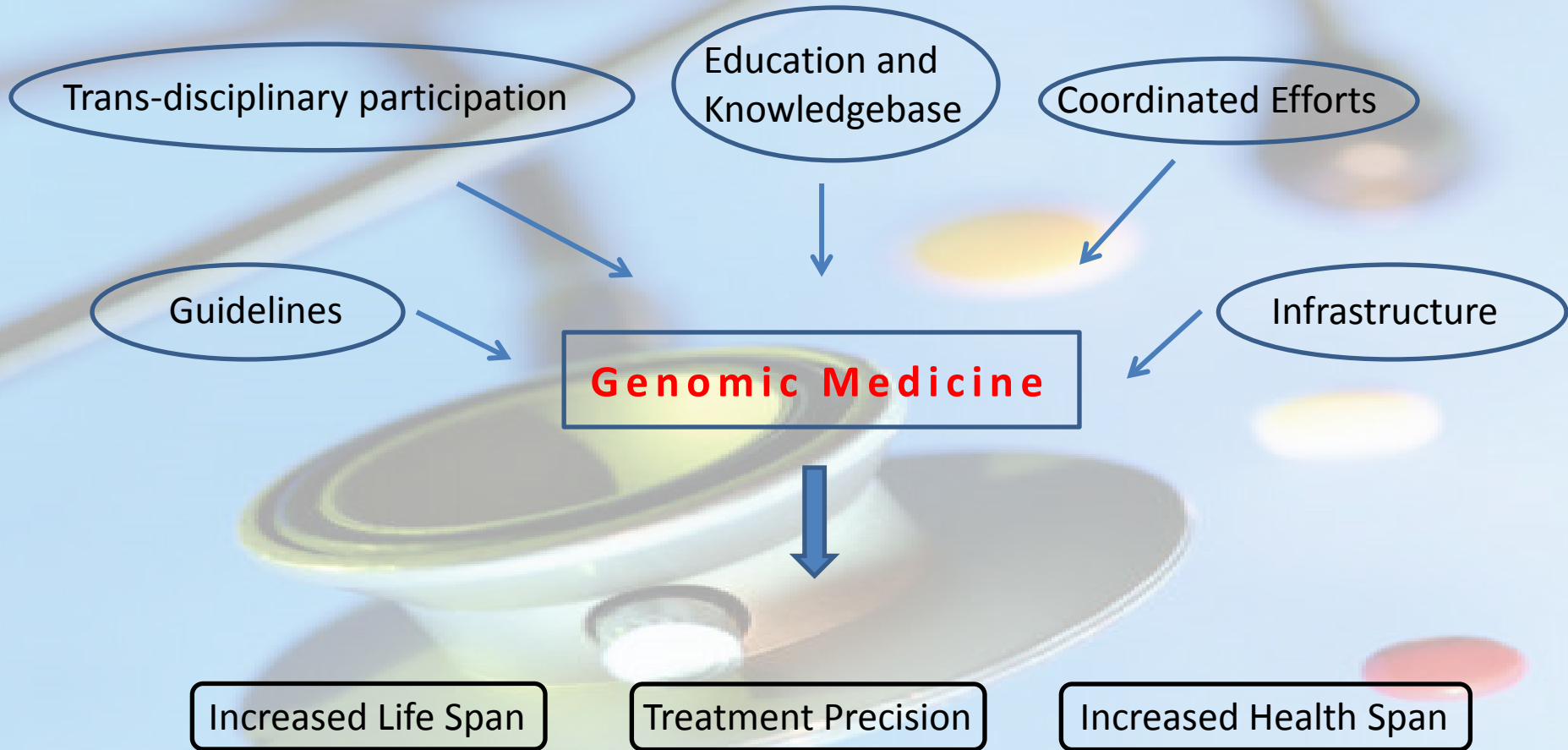
- ❖ **Strategy: Benefits and targets in Indian Context**
- ❖ **Implementation of Genomic Medicine in India : DBT initiatives**
- ❖ **Hurdles in Implementation**
- ❖ **Collaborations**

A stethoscope is positioned diagonally across the frame, with its chest piece in the lower-left foreground and its earpieces extending towards the upper-right. Several pills of different colors (yellow, white, red) are scattered on the light blue background. The overall scene is softly lit, creating a professional and medical atmosphere.

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FOCUS



AREAS LIKELY TO BE BENEFITTED

Diseases

- Adult onset
- Rare diseases

Prediction

- Adverse drug effects
- Pregnancy

Diagnostics

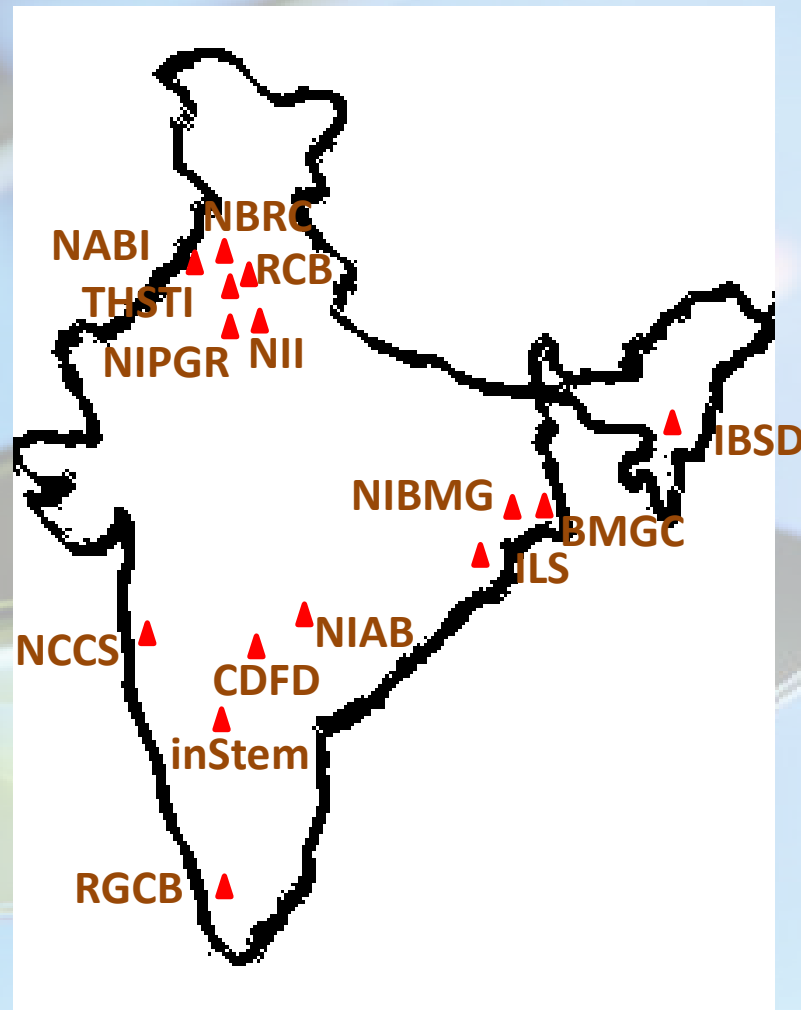
- Point of care
- Affordable
- Novel

Increased Knowledge

- Integrated body functioning
- Organismal adaptability to genetic changes
- Translational research boost

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INFRASTRUCTURE DEVELOPMENT AT INSTITUTES FOR ADVANCED GENOMIC RESEARCH AND PHARMACOGENOMICS IMPLEMENTATION



GENETIC CATALOGUING OF ETHNIC GROUPS

Data coordination

1. Clinicians
2. Molecular Geneticists
3. Anthropologists

Creation of baseline data on various ethnic groups for disease susceptibility

PROMOTING TRANSLATIONAL RESEARCH

A stethoscope is positioned diagonally across the frame, with its chest piece resting on a light blue surface. To the right of the stethoscope, a single red pill is visible. The background is a soft, light blue gradient.

- ✓ Diagnostic kits
- ✓ Vaccines using reverse genetics
- ✓ Molecular tool for surveillance
- ✓ Control of Newcastle disease by siRNA mediated inhibition of virus
- ✓ Disease based sequence analysis

PRE-NATAL CARE



- ✓ Maternal risk and pregnancy risk prediction
- ✓ Fetal Risk Prediction and anomaly diagnosis
- ✓ initiating programs involving Developmental biology, Pregnancy Risks and Pre-term Birth
- ✓ Setting up of Genetic Clinics

CANCER GENOMICS

A stethoscope is positioned diagonally across the frame, with its chest piece in the lower-left foreground and its ear pieces extending towards the upper-right. Several pills are scattered on the light blue background: a yellow pill near the chest piece, a white pill near the ear pieces, and a red pill in the lower-right corner. The background is a soft, light blue gradient.

- ✓ Genomics and Epigenomics of Cancer
- ✓ Transcriptomics of Cancer
- ✓ NIBMG is a part of the International Cancer Genome Consortium (Oral Cancer)

OTHER AREAS

- ✓ Strengthening of bioinformatics network by creating Genome Mirror sites
- ✓ Regulatory guidelines for Genomic Medicine techniques, research activities and harmonisation with international ethical guidelines (National Bioethics Committee- DBT nodal agency).
- ✓ Manpower training in various aspects of Genomic Medicine
- ✓ Establishment of transformed cell line for rare and genetic diseases and their genetic analysis
- ✓ Funding of research in areas like genotype-phenotype correlation in oxidative stress related gene polymorphisms, DNA repair proteins, mutation screening in Congenital Adrenal Hyperplasia, finding drug targets in *P.falciparum*, diagnosis using pharmacogenetic tools, biomarkers, cancer genomics

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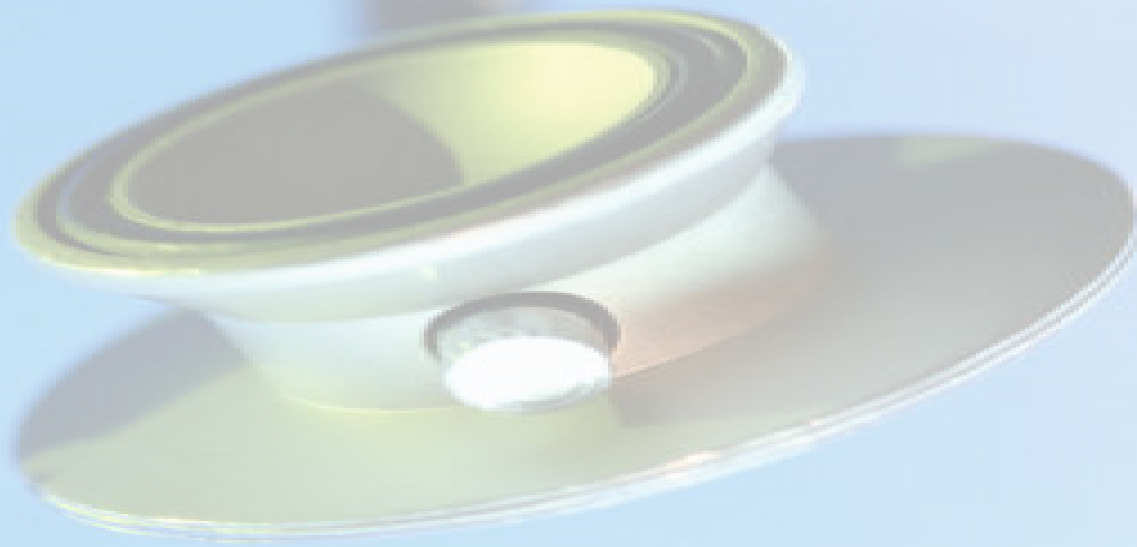
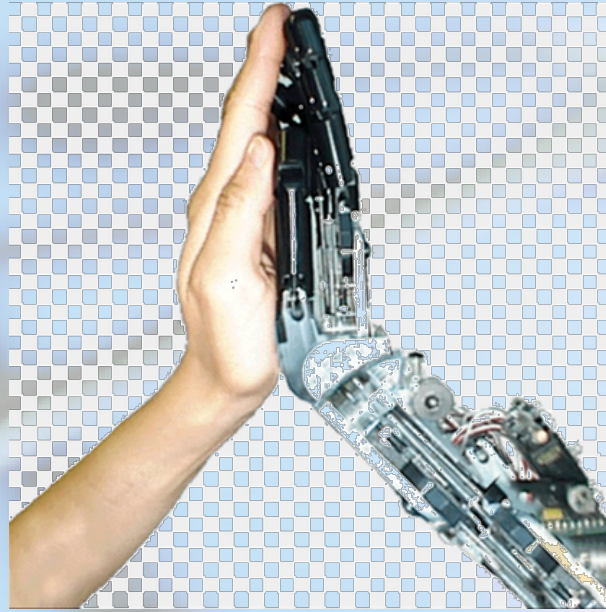
COMMON BARRIERS IN IMPLEMENTATION

- ✓ Handling large dataset
- ✓ Evidence for health treatments are based on research goals
- ✓ Research waste due to lack of expertise
- ✓ Lack of regulatory guidelines
- ✓ Incidental findings majorly
- ✓ Lack of knowledge in primary healthcare providers
- ✓ Need for better technologies
- ✓ Large dataset for patients and lack of translation/interpretation
- ✓ Funding and political will

- 
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POSSIBLE AVENUES FOR COLLABORATION

- ✓ Streamlining of guidelines for implementation and preclinical/clinical trials
- ✓ Use of traditional knowledge and integration into modern genetics
- ✓ Cloudsourcing for translation of genetic data
- ✓ Development of new methods of disease classification based on recently discovered genetic principles
- ✓ Building community interest and participation
- ✓ Building data sharing capabilities
- ✓ Unify strategies ongoing at various places
- ✓ Set up biobanking facilities
- ✓ Training of Manpower
- ✓ Building study cohorts



THANK YOU

Over to

PARTHA MAJUMDER

**National Institute of Biomedical Genomics
Kalyani, India**

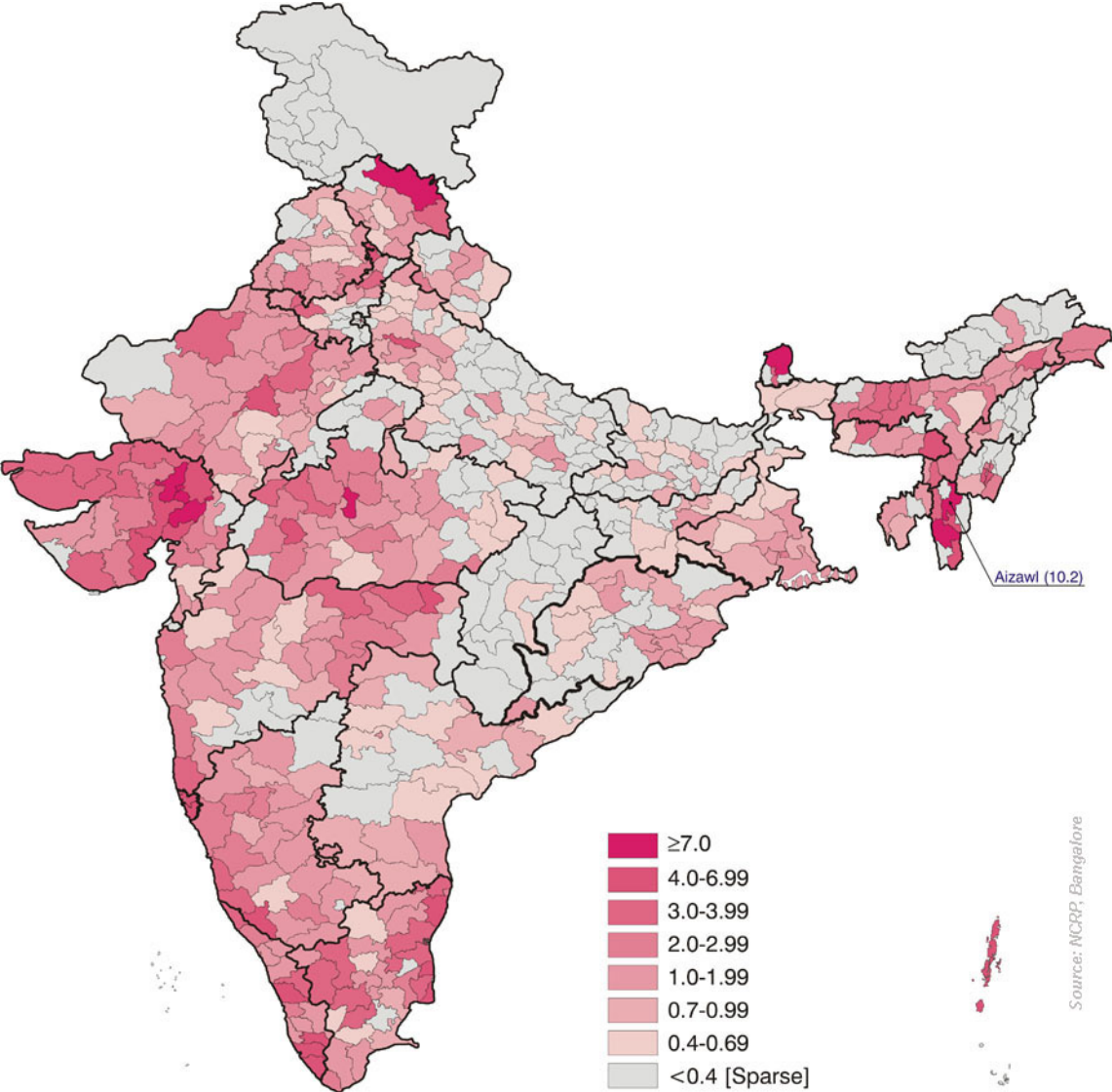
Genetic Epidemiology of Cancer in India

CANCER ATLAS OF INDIA

**Indian Council of Medical Research
*(in collaboration with WHO)***

1980-2000

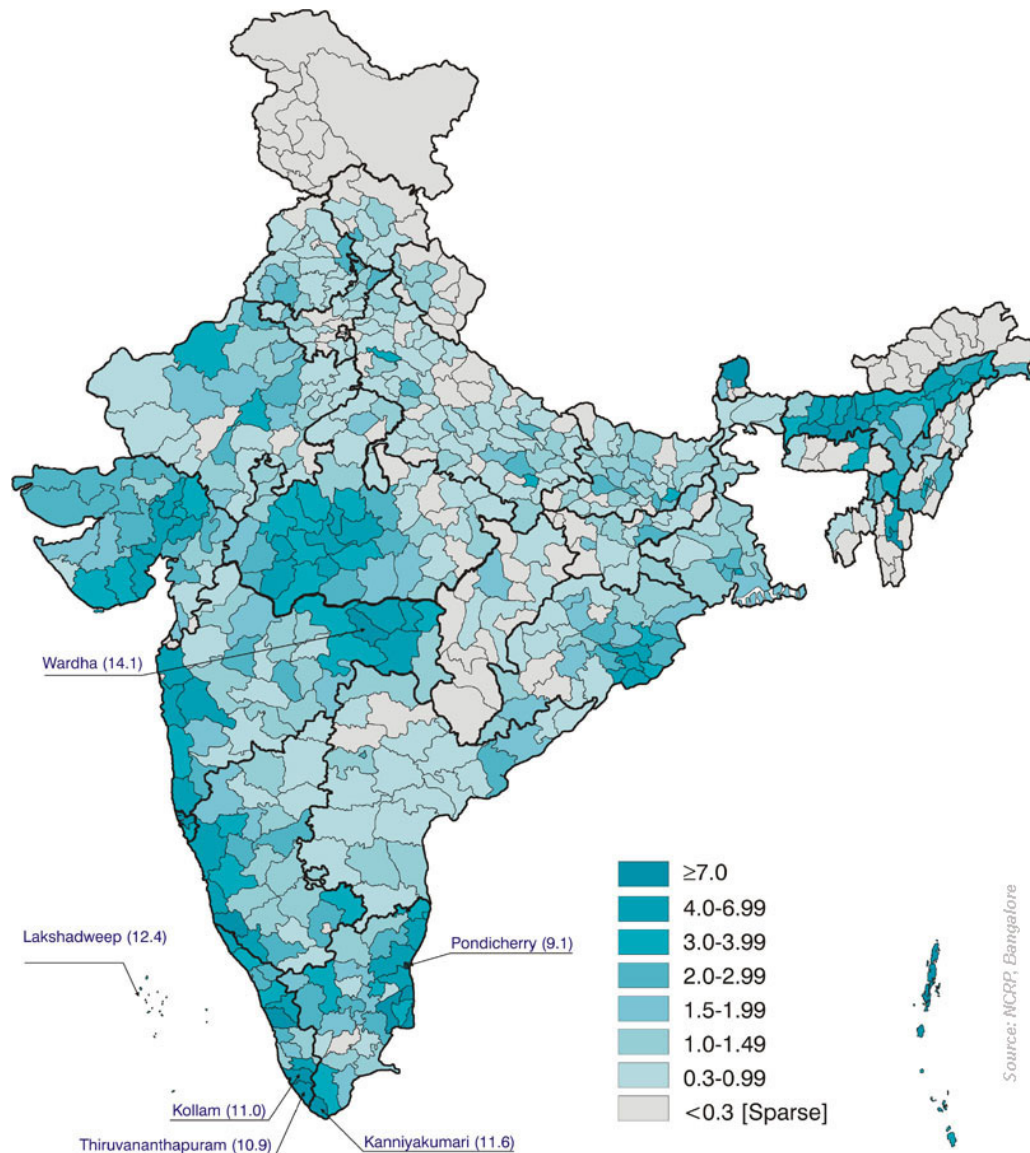
Districtwise Minimum Age Adjusted Incidence Rate Per 100,000 **TONGUE** (ICD10,C01-C02) - Males



Districtwise Minimum Age Adjusted Incidence Rate Per 100,000

MOUTH

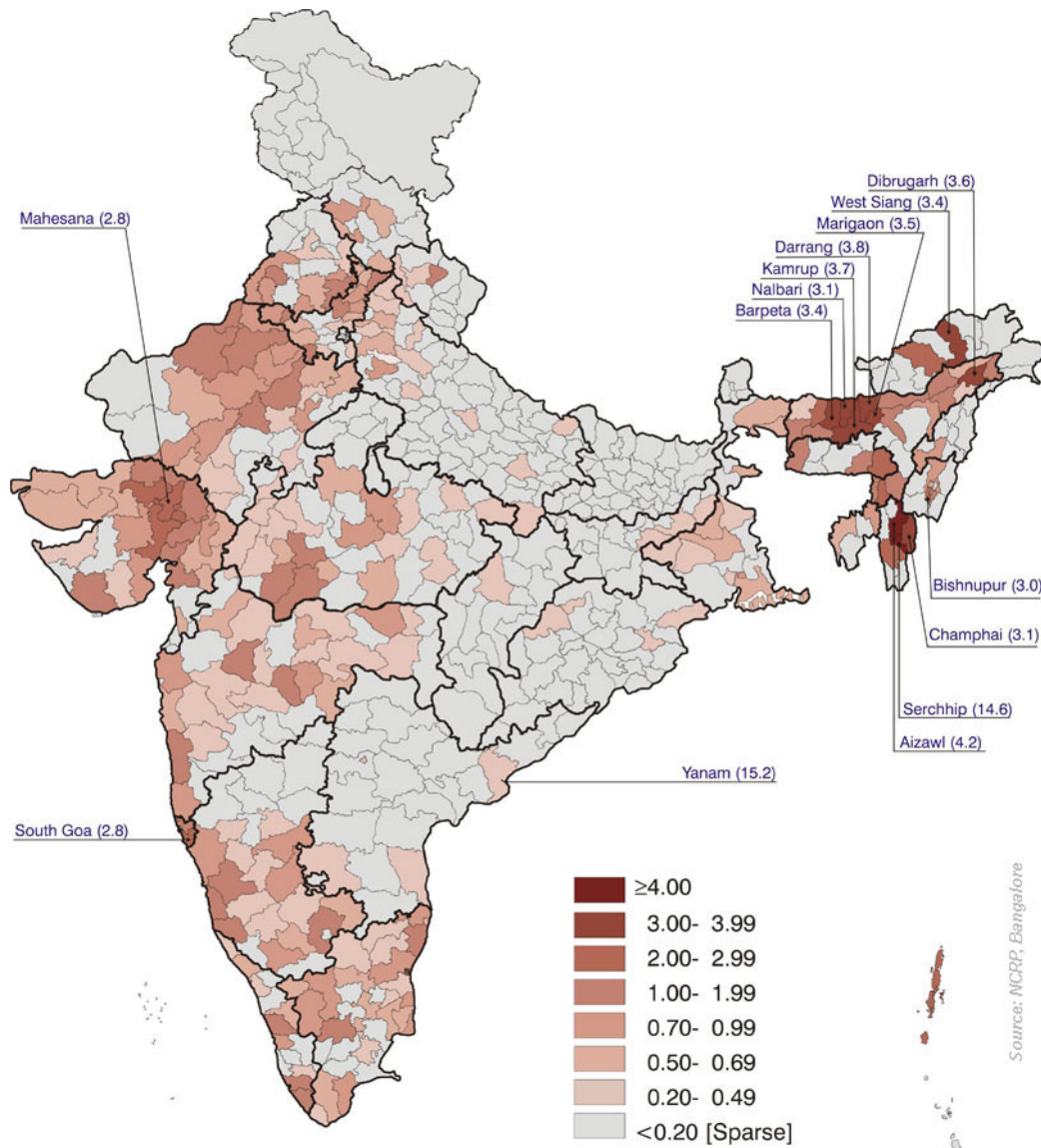
(ICD10, C03-C06) - Males



Districtwise Minimum Age Adjusted Incidence Rate Per 100,000

TONSIL

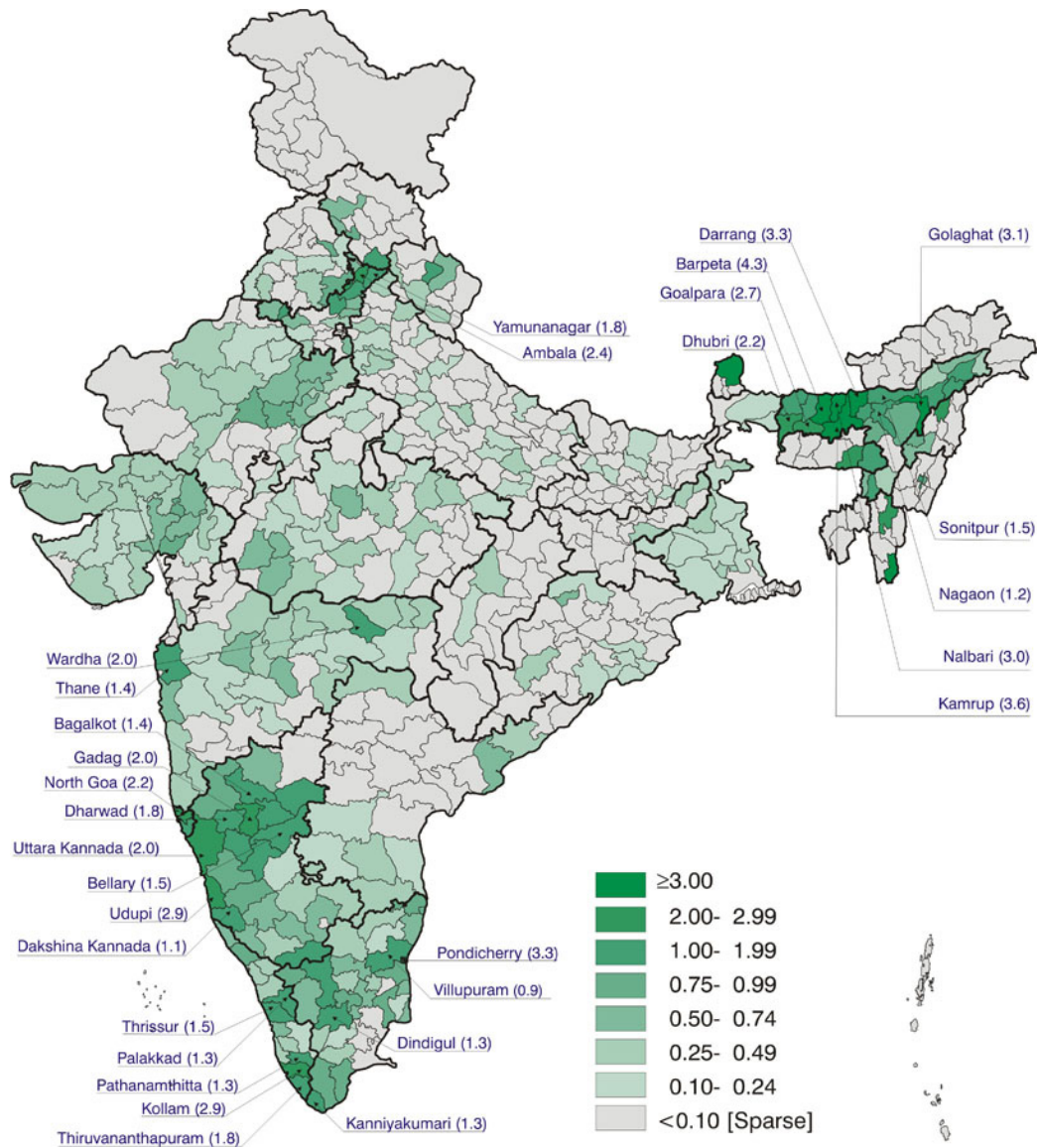
(ICD10, C09) - Males



Districtwise Minimum Age Adjusted Incidence Rate Per 100,000

OROPHARYNX

(ICD10, C10) - Males



Institutions involved in Cancer Research

Clinical cum Basic

- 1. All India Institute of Medical Sciences (AIIMS), New Delhi**
- 2. Kidwai Memorial Institute of Oncology (KMIO), Bengaluru**
- 3. Tata Memorial Hospital (TMH), Mumbai**
- 4. Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Mumbai**
- 5. Cancer Institute (WIA), Chennai**
- 6. Rajiv Gandhi Center For Biotechnology (RGCB), Thiruvananthapuram**
- 7. Institute of Cytology & Preventive Oncology (ICPO), Noida**

Basic Biology of Cancers

- 1. National Centre for Cell Sciences (NCCS), Pune**
- 2. National Brain Research Centre (NBRC), Manesar**
- 3. National Centre for Biological Sciences (NCBS), Bengaluru**
- 4. National Institute of Immunology (NII), New Delhi**
- 5. Mazumdar Shaw Cancer Center (MSCC), Bengaluru**
- 6. Indian Institute of Science (IISc), Bengaluru**
- 7. Institute of Life Sciences, Bhubaneshwar**

Adjunct Facilities

- 1. C-CAMP, Bengaluru**
- 2. Institute of Bioinformatics, Bengaluru**
- 3. C-DAC, Pune**

**Slide Courtesy:
Dr. Bindu Dey, Adviser, DBT**

Focus of Research

Based on Disease-burden

- Oral/Head & Neck cancer
- Cervical cancer
- Breast cancer sp. triple-negative, pre-menopausal cancer

Uniqueness to India

- Nasopharyngeal cancer- NER
- Gall Bladder cancer- Along Ganges belt; mostly in women
- Gastric cancer from Nagaland (Naga cancer)/Kashmir

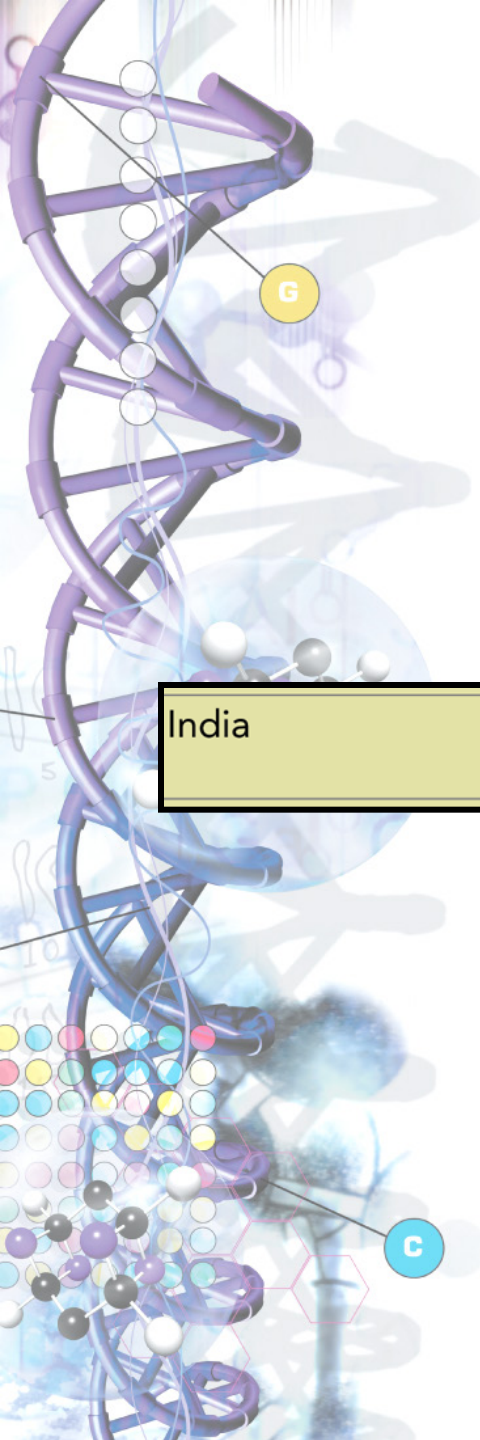
Competence availability

- Gliomas (funding primarily by CSIR)
- Leukemias

Work initiated

- Lung cancer
- Pancreatic cancer

Slide Courtesy:
Dr. Bindu Dey, Adviser, DBT



Lead Jurisdiction	Funding Organization	Tumor Type
Australia	National Health and Medical Research Council	Pancreatic Cancer Ductal adenocarcinoma Ovarian Cancer Serous adenocarcinoma
Canada	Ontario Institute for Cancer Research Ontario Ministry of Research and Innovation	Pancreatic Cancer Ductal adenocarcinoma
China	Chinese Cancer Genome Consortium	Gastric Cancer Intestinal- and Diffuse-type
European Union/France	European Commission FP7	Renal Cancer Renal cell carcinoma Focus on but not limited to clear cell subtype
European Union/ United Kingdom	European Commission FP7	Breast Cancer Subtypes defined by an amplification of ER+ HER- ductal-type
France	Institut National du Cancer	Breast Cancer HER2 positive Liver Cancer Hepatocellular carcinoma Secondary to alcohol and adiposity
Germany	Federal Ministry of Education and Research German Cancer Aid	Pediatric Brain Tumors Medulloblastoma

India

Department of Biotechnology,
Ministry of Science & Technology

Oral Cancer
Gingivobuccal

	Indian Ministry of Education, University and Research	Enteropancreatic endocrine tumors and rare pancreatic exocrine tumors
Japan	RIKEN National Institute of Biomedical Innovation	Liver Cancer Hepatocellular carcinoma Virus associated
Spain	Spanish Ministry of Science and Innovation	Chronic Lymphocytic Leukemia CLL with mutated and unmutated IgVH
United Kingdom	Wellcome Trust Breakthrough Breast Cancer	Breast Cancer Triple Negative/Lobular/Other
United States	National Institutes of Health	Brain Cancer Glioblastoma multiforme Ovarian Cancer Serous cystadenocarcinoma Lung Cancer Squamous cell carcinoma Adenocarcinoma Leukemia Acute myeloid leukemia Colon Cancer Adenocarcinoma

ICGC Cancer Genome Projects

TCGA Projects

ome Projects

ICGC Cancer

Squamous Cell Carcinoma of the Oral Cavity: Epidemiological Features

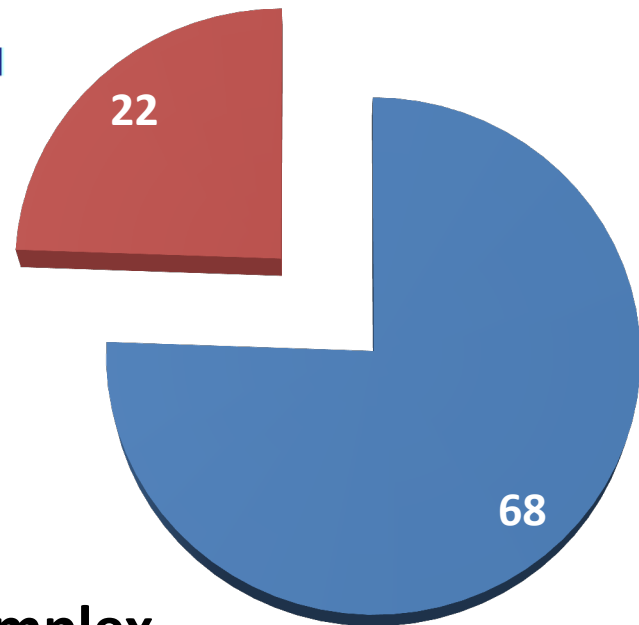
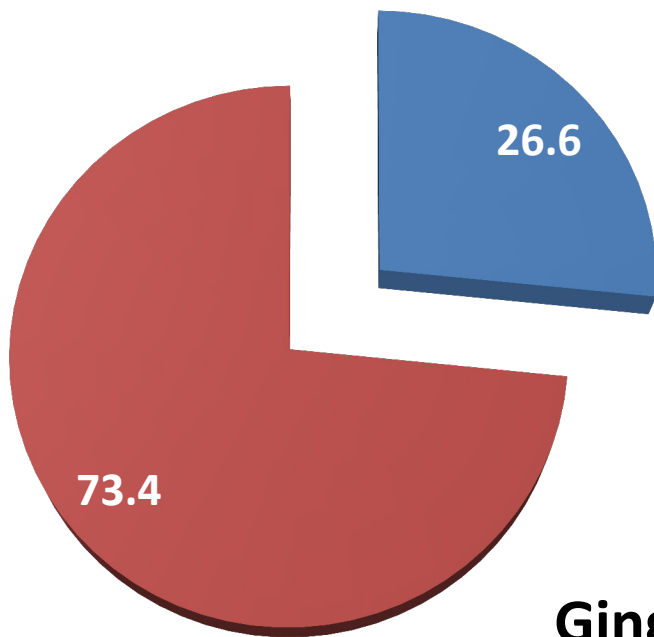
- 8th most common cancer**
 - ~260,000 new cases annually**
 - 2/3rd in developing countries**
 - 128,000 deaths annually**
-
- Accounts for ~1/3rd of all tobacco-related cancers in India.**

Site Distribution of Oral Cancer

INDIA

WEST

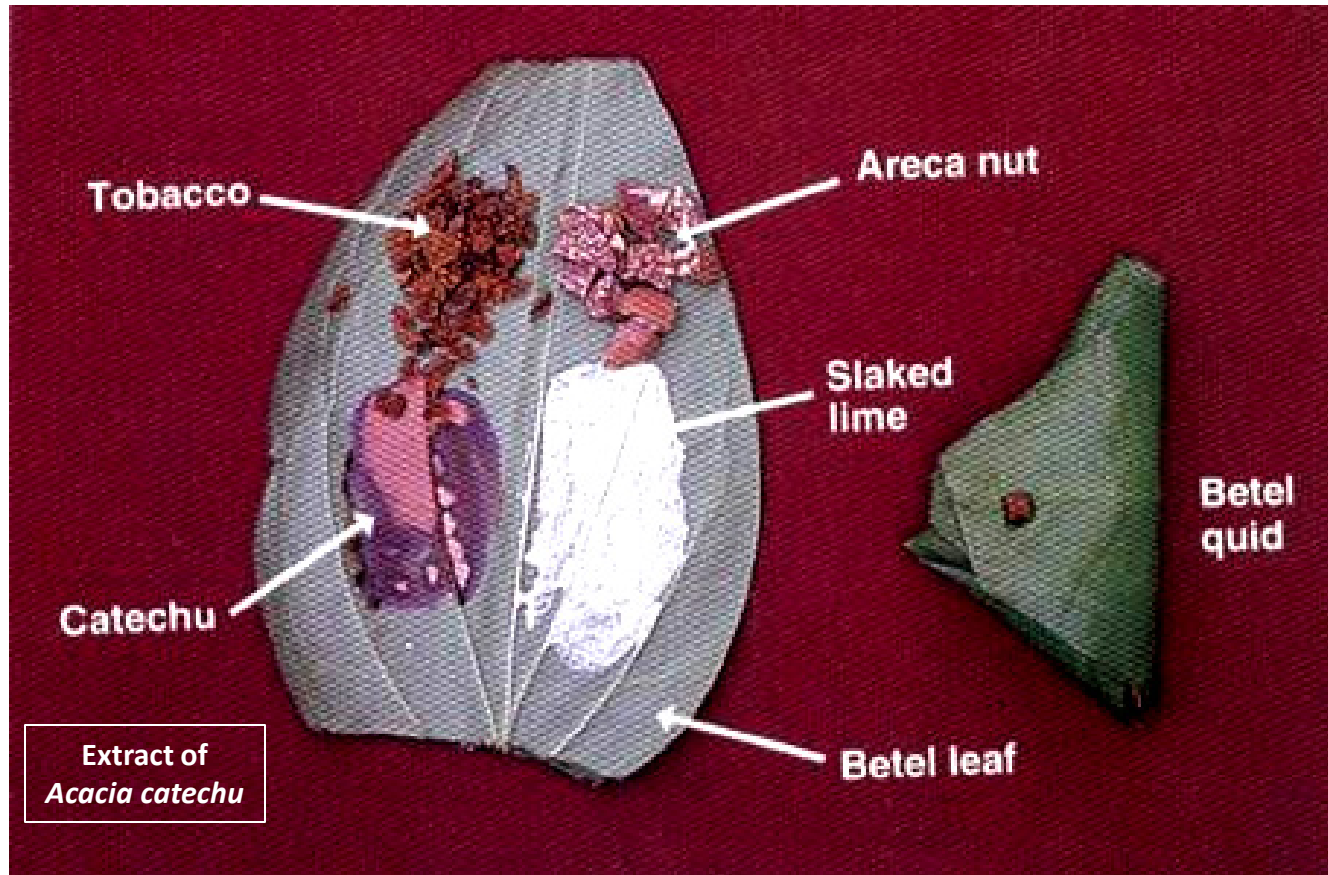
- Tongue & Floor of Mouth
- Gingivobuccal Complex



Gingivobuccal Complex

Buccal Mucosa, Lower Gum, Retromolar Trigone (RMT)

The Hazardous Combo



GENES SIGNIFICANTLY MUTATED

Gene	p-value
<i>CASP8</i>	$<10^{-13}$
<i>TP53</i>	$<10^{-13}$
<i>FAT1</i>	4.10×10^{-13}
<i>HRAS</i>	3.42×10^{-05}
<i>ARID2</i>	1.85×10^{-04}
<i>TRPM3</i>	1.84×10^{-03}
<i>UNC13C</i>	1.90×10^{-03}
<i>USP9X</i>	2.56×10^{-03}
<i>MLL4</i>	1.22×10^{-02}
<i>NOTCH1</i>	1.43×10^{-02}

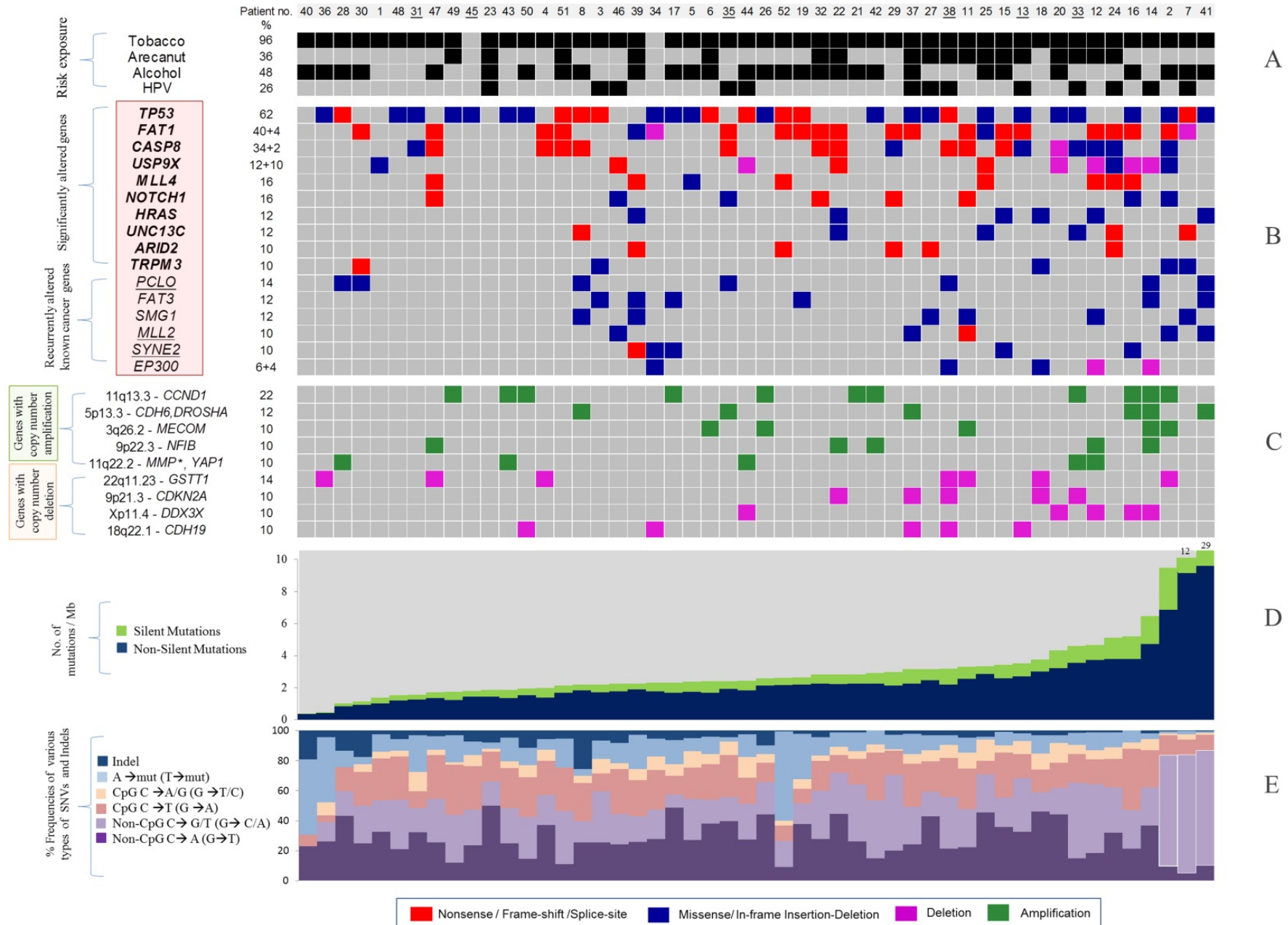
Discovery Sample Size = 50 patients

Validation Sample Size = 60 patients

Pathways Most Significantly Altered

Description of pathway	No. of patients affected	p-value	% of genes altered in pathway
p53 signaling pathway	36	4.87E-09	41.2
Apoptosis	37	5.21E-09	42.0
Viral carcinogenesis	39	2.12E-06	36.7
Neurotrophin signaling pathway	40	7.12E-06	41.7
Wnt signaling pathway	39	0.00095	37.7

Profile of 'Significant' Genomic Alterations



***CCND1, FADD, CDH6, CDH10,
DROSHA, MECOM, NFIB,
MMP gene cluster, YAP1***

Gene Completely Deleted

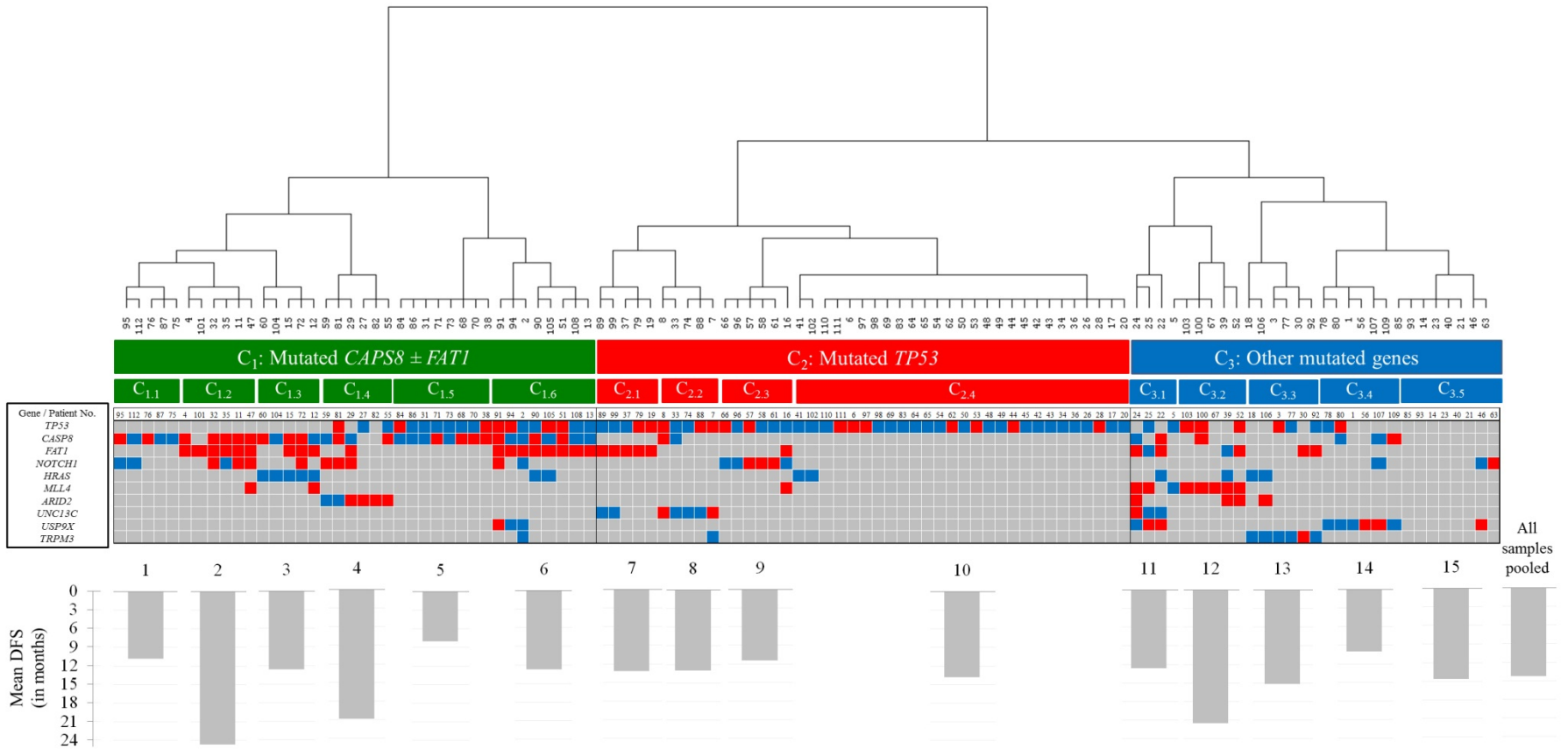
GSTT1

Genes (Exons) Partially Deleted

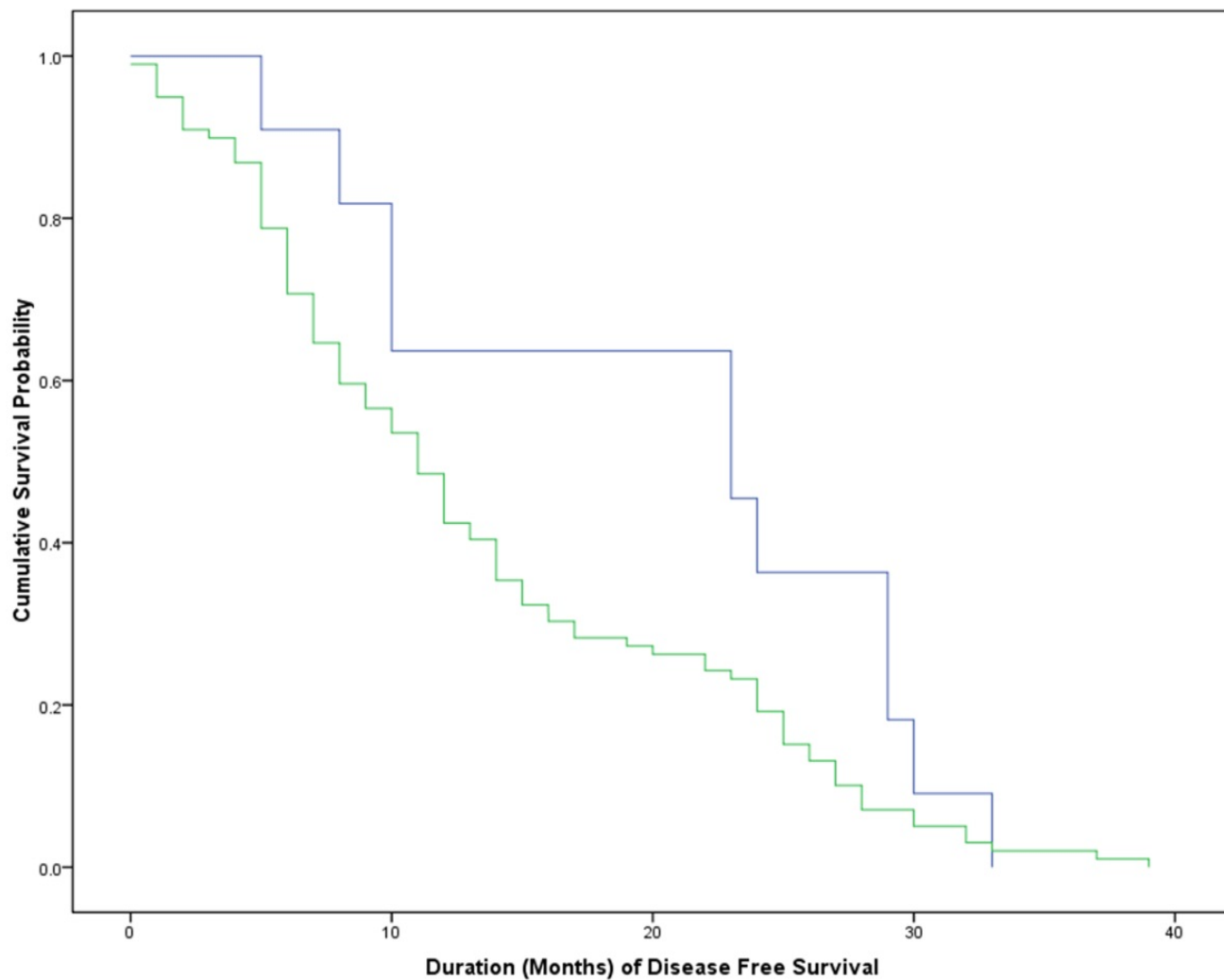
CDKN2A, DDX3X, CDH19

**We obtained evidence of whole genome duplication
in at least 7 tumor samples (Ploidy > 4n).**

Patients Form 3 Groups by the Spectra of Mutations



Patients with Mutations in *MLL4* Have Longer Disease Free Survival



With mutation (GREEN line): 20.4 \pm 3.1 months
Without mutation (BLUE line): 13.5 \pm 0.9 months
 $p=0.047$

ARTICLE

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OPEN

Mutational landscape of gingivo-buccal oral squamous cell carcinoma reveals new recurrently-mutated genes and molecular subgroups

India Project Team of the International Cancer Genome Consortium¹